Part I. The Structure of 1,2-Dimethylnorbornyl Cation

Part II. The Relative Stabilities of Some Tertiary Aliphatic Cations

Thesis by

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Abstract

Part I

The pmr spectrum of 1,2-dimethylnorbornyl cation indicates that the Wagner-Meerwein rearrangement is rapid on the nmr time scale at -100° C. Furthermore the protons at C-6 are deshielded by 1.3 ppm with respect to the protons at C-5. This is consistent with the nonclassical structure for this cation.

Part II

Mixtures of organic chlorides have been forced to compete for less than one equivalent of antimony pentafluoride in order to judge relative cation stabilities. The results indicate no stabilization of 2,3,3-trimethyl-2-butyl cation by methyl bridging. However methylene bridging seems to stabilize 1,2-dimethylnorbornyl cation. The qualitative order of cation stabilities measured by this method is not always the same as that measured by solvolysis experiments.

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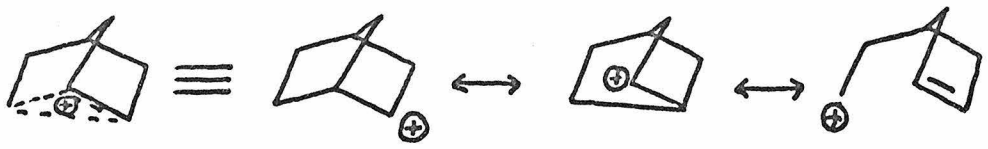
To Judy and Kevin

INTRODUCTION

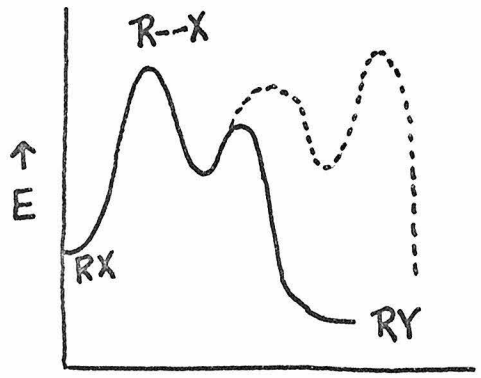
In 1952 Winstein proposed that the intermediate in the solvolysis of 2-exo-norbornyl arylsulfonates is a symmetrical nonclassical ion, I.



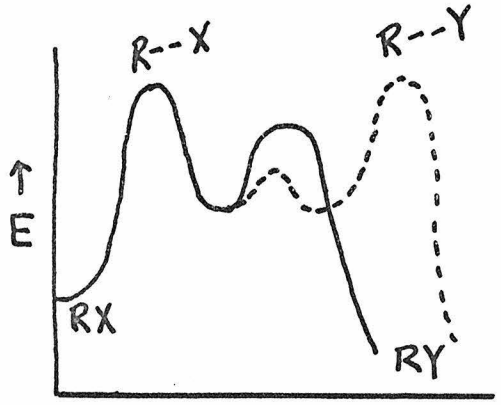
I

This proposal was based on the accelerated solvolysis rate of the exo-norbornyl arylsulfonate compared to cyclohexyl arylsulfonate and on the stereospecificity of the attack on the cation (1,2,3). Presumably the acceleration in rate of reaction reflects increased cation stability, and the specificity of attack by the nucleophile is a consequence of carbon bridging.

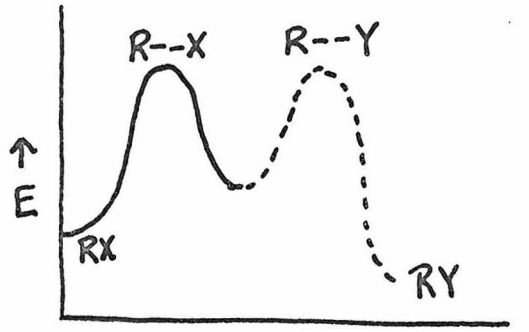
H. C. Brown suggested three kinds of carbonium ions: classical static ions, classical equilibrating ions, and nonclassical bridged ions.



classical static
(a)



classical equilibrating
(b)

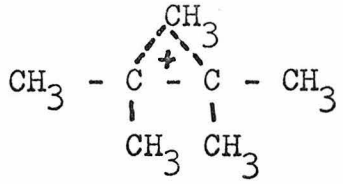


nonclassical bridged
(c)

Figure 1

In the case of the static ions (a), the energy barrier for equilibration of two symmetrical cations is higher than that for conversion to products. Equilibration between ions takes place in case (b) because the energy barrier for this process is lower than the barrier leading to products. In the nonclassical bridged ion, the barrier has disappeared, and the ion is stabilized by charge delocalization. Brown has urged a re-examination of all ions considered to be nonclassical to see if they can be assigned to the classical equilibrating group (4).

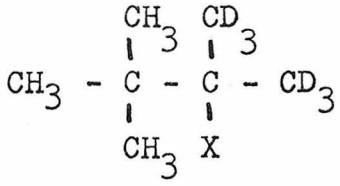
A nonclassical structure was considered for the 2,3, 3-trimethyl-2-butyl cation (II), but labeling work proved that this type of methyl bridging was not important.



II

Treatment of 2,3,3-trimethyl-2-butanol-1-^{14}C with concentrated hydrochloric acid gives only 12% rearrangement after one minute. Nearly 58% rearrangement is observed under reversible conditions where 100% of the chloride product has exchanged with hydrochloric acid. These results indicate that methyl bridging is not important under irreversible conditions (5).

This result has been confirmed in deuterium labeling studies on III. Very little scrambling of the deuterium label occurs,



III

indicating only a small amount of equilibration relative to solvent capture.

reaction	% scrambling
III-OH + HCl $\xrightarrow{H^+}$ III-Cl + H_2O	12
III-OH + CH_3OH $\longrightarrow$ III-OCH_3 + H_2O	26
III-Cl + CH_3OH $\longrightarrow$ III-OCH_3	19

Figure 2

These reactions are usually considered to involve carbonium ion intermediates; therefore, the conclusion that bridging is unimportant seems valid (6).

The question of methylene bridging in a more sterically favorable bicyclic tertiary cation has been extensively studied. The 1,2-diarylnorbornyl cation seems

to be a classical ion with the positive charge localized on one carbon. The ultraviolet spectrum, chemical reactivity, and thermodynamic stability of the monoaryl- and 1,2-diarylnorbornyl cations are quite similar. The pmr spectrum at high temperature shows a single aryl peak which loses detail and broadens at -20° C., indicating impending nonequivalence (7).

H. C. Brown has examined 2-methyl- and 1,2-dimethylnorbornyl derivatives to see if these cation systems are classical. He criticized the use of t-butyl or cyclohexyl derivatives as model compounds in those anchimeric assistance studies which show rate increases for solvolysis of norbornyl derivatives (1,2,3). Instead, he prefers methylcyclopentyl compounds as models. The rate of solvolysis of 2-methyl-2-exo-chloronorbornane is only five times as great as that of the model compound, 1-chloro-1,2-dimethylcyclopentane. Such a small rate increase indicates no significant participation by the 1,6 sigma bond (8).

Another argument favoring a classical 2-methylnorbornyl cation is that introduction of a methyl group has a large effect on solvolysis rates in the norbornyl system but a much smaller effect on a resonance delocalized system (Figure 3). Brown's conclusion is that norbornyl cation does not behave like a resonance stabilized cation (9).

Equilibration of 2-methyl-exo-norbornyl alcohol,

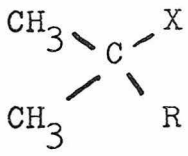
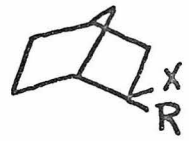
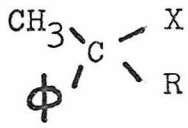
	R=H X=OTS EtOH	H OTS HOAc	H C1 EtOH	Me C1	kMe kH
	0.0184	0.081	1.57×10^{-6}	0.086	55,000
	0.377	1.66	3.21×10^{-5}	5.62	175,000
	5.55	24.4	5.42×10^{-4}	30.0	55,000
			0.216	394	1,800

Figure 3

2-methyl-endo-norbornyl alcohol, and 1-methyl-2-exo-norbornyl alcohol in perchloric acid-water-dioxane gives an equilibrium product distribution of 1.3:1.0:3.6. The same experiment on 1,2-dimethyl exo- and endo-norbornyl alcohol gives an exo to endo ratio of 2.6:1.0. Furthermore, the rate of formation of the 2-methyl-2-exo-norbornyl alcohol is twice that for formation of 1-methyl-2-exo-norbornyl alcohol. Brown takes these facts as evidence that the rate of capture of 2-methylnorbornyl cation is much faster than the Wagner-Meerwein rearrangement to the secondary 1-methylnorbornyl cation. This is more evidence that 2-methylnorbornyl cation is a classical tertiary ion in equilibrium with a small amount of secondary ion (10).

Hydrochlorination of 1-methylnorbornene gives a 45:55 distribution between 3-chloro-1-methylnorbornane and 2-chloro-2-methylnorbornane. Brown argues that these data are inconsistent with a delocalized cation in which the methyl group would have a much larger directive effect in the reaction (11).

Brown argues that since the 2-methyl-2-norbornyl cation is classical, the introduction of a methyl group at C-1 should have a very large effect if the 1,2-dimethylnorbornyl cation is nonclassical. Furthermore, this large substituent effect should be observed in the exo but not the endo derivatives. The results are shown in Figure 4.

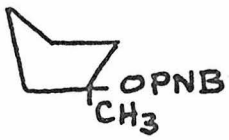
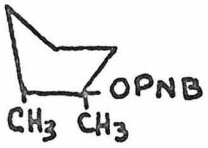
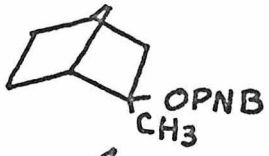
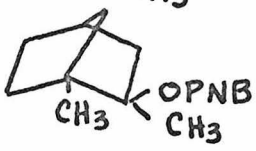
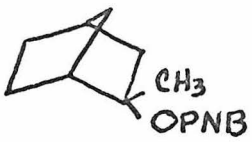
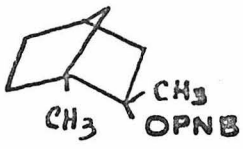
Compound	(50°)rate constant x 10^{6} sec^{-1}	Me/H rel.rates	exo/endo
	0.50	1.00	
	1.16	2.3	
	1.67	3.4	183
	2.2	1.00	165
	9.4	4.3	
	0.012	1.00	
	0.057	4.8	

Figure 4

The data indicate that 1,2-dimethylnorbornyl cation is classical (12).

Finally Brown has studied the hydrochlorination of 1-methyl-d_3-2-methylenenorbornane to see if C-1 and C-2 become equivalent, as demanded for a nonclassical ion. Using neat olefins and very short reaction times, scrambled products amount to 35% of total. In ether or methylene chloride, scrambling as low as 52% is observed. The experiment gives equivalent results with 1-methyl-2-methylene-d_2-norbornane. Equilibration is not complete, so 1,2-dimethylnorbornyl cation is in the classical equilibrating category of cations (13).

Even though 2-methyl- and 1,2-dimethylnorbornyl cations are classical, they show high specificity for exo-substitution (14) (Figure 5) and high exo and endo rates of solvolysis (Figure 4). Brown points out that exo substitution and high exo:endo rate ratios are therefore not good criteria for formation of nonclassical ions.

Generation of norbornyl, 2-methylnorbornyl, and 1,2-dimethylnorbornyl cations through the π route from 2-(Δ^3-cyclopentenyl) ethyl p-nitrobenzoates (IV) seems to indicate a delocalization of charge over both C-1 and C-2. The effect of the first methyl substitution, V, in this system is a 7.0-fold increase in rate over the unsubstituted compound. Addition of another methyl group, VI, gives a rate increase of 5.5. The products from the solvolyses are

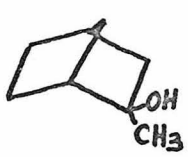
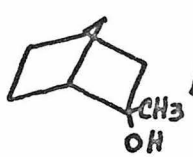
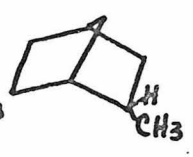
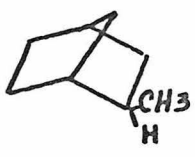
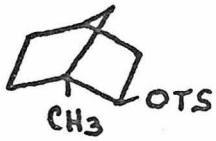
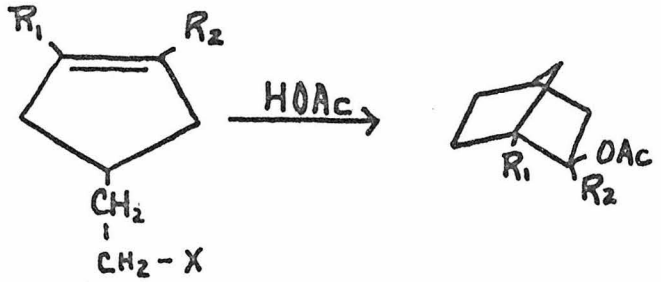
	% products					
						
(NaBH$_4$ added as trapping agent)						
	57	0	35	0.5	3	3
	56	0	42	0.6	0.8	0.8

Figure 5

2-methyl-2-exo-norbornyl acetate from V and 1,2-dimethyl-exo-norbornyl acetate from VI.



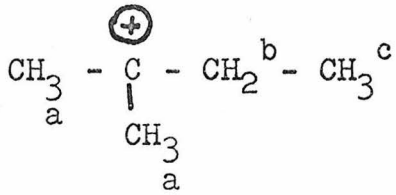
IV $R_1=R_2=H$

V $R_1=H$; $R_2=CH_3$

VI $R_1=R_2=CH_3$

These data seem to be inconsistent with Brown's classical 1,2-dimethylnorbornyl cation which has the charge localized on only one carbon. If this were the case, the second methyl substitution should be much less effective in stabilizing the transition state (15).

G. A. Olah has had much success observing alkyl cations in sulfur dioxide solutions of antimony pentafluoride. The cations are generated from alkyl halides in this highly ionizing solution. In this manner, t-butyl cation can be generated from t-butyl fluoride. The methyl groups appear as one singlet at -4.07 ppm from TMS. In the same manner, t-amyl cation can be generated from t-amyl fluoride; the pmr spectrum of cation VII consists of a triplet at

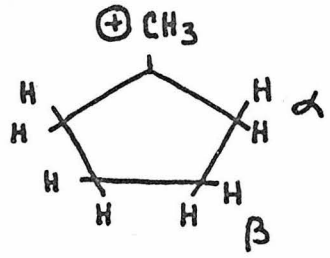


VII

-1.72 ppm, a triplet at -3.97 ppm, and a septet at -4.30

ppm from TMS. The upfield triplet is assigned to protons c, the low field triplet to protons a, and the septet to b. The long range coupling between the methyl and methylene groups through the sp^2 carbon is about 7 cps. The spectrum of isopropyl cation consists of a methyl doublet at -5.05 and a methine septet at -13.5 ppm (neat SbF_5, no SO_2 added) (16).

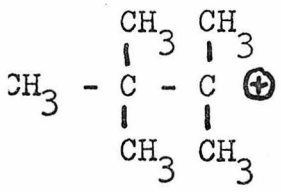
Methylcyclopentyl cation (VIII) is also of interest to this study. The spectrum is quite complex, consisting of an upfield quintet at -2.47 ppm which is assigned to the β-methylene protons.



VIII

The low field multiplet is assigned by analogy to the methyl and methylene protons in t-amyl cation. The methyl protons are at -3.98 ppm and the α-methylene protons at -4.20 ppm. A long range coupling constant of 4.0 cps is assigned for coupling between the methyl and α-methylene protons. The methylcyclopentyl cation is generated from either methylcyclopentyl or cyclohexyl halides or alcohols (17).

Another interesting tertiary cation is the 2,2,3-trimethyl-2-butyl cation (IX). The spectrum of IX consists of a singlet at -2.86 ppm.



IX

All the methyl groups are equivalent as low as -180° C. At -10° C. the ion cleaves to give t-butyl cation. Olah has assigned a classical equilibrating structure to the cation because he feels the methyl resonance of a protonated tetramethylcyclopropane would occur at high field due to anisotropy from the cyclopropyl ring and delocalization of the positive charge. The model he uses for the nonclassical bridged system is tetramethylethylene halonium ion, where the methyl shift is 0.95-0.75 ppm. He assigns the barrier to methyl rearrangement as less than 2-3 kcal/mole (18).

The tricyclic adamantyl and bicyclic norbornyl cations will also be of interest in later discussion. The adamantyl cation (X)

X

spectrum consists of a lowfield γ-proton resonance at -5.42 ppm, a β-proton resonance at -4.50 ppm, and a δ-proton resonance at -2.67 ppm. The interesting point is that the γ-protons are deshielded with respect to those β to the positive charge. Olah considered the possibility that an intermolecular hydride shift by the γ protons might explain the deshielding but discounted this on the basis of temperature independence of the spectrum from +40 to -90° C. This leaves charge delocalization by hyperconjugation and backside overlap between the C-H sp^3 orbitals and the empty p orbital to explain the deshielding. Olah prefers delocalization by backside overlap (19).

The pmr spectrum of norbornyl cation consists of a single peak at -3.1 ppm. On cooling to -60° C. this peak splits into three peaks at -5.35 ppm (area 4), -3.15 ppm (area 1), and -2.20 ppm (area 6). This is explained by a slow 3,2 hydride shift, which is frozen out in the low temperature spectrum. Cooling as low as -143° C. produced no further change in the spectrum. On this basis, the maximum barrier to Wagner-Meerwein rearrangement and 1,6 hydride shifts is assigned as 5.5 kcal/mole (20).

It seemed desirable to study the pmr spectra of the 1,2-dimethylnorbornyl and 2-methylnorbornyl cations. The pmr spectrum of the 1,2-dimethyl ion should allow the study of Wagner-Meerwein rearrangement in the absence of significant amounts of 1,6 and 2,3 hydride shift to less stable

secondary cations. The spectra should also shed some light on on the nature of the charge distribution in tertiary norbornyl cations. This information has bearing on the question of whether tertiary norbornyl cations are classical.

RESULTS

The dimethylnorbornyl cation was prepared either from a mixture of 1,2-dimethyl-2-exo- and endo-norbornyl chlorides or from the exo or endo alcohols. The 1,2-dimethyl-2-endo-norbornyl alcohol and 1,2-dimethyl-2-exo-norbornyl alcohol were prepared and the spectra recorded (21,22). The pmr spectrum of the exo isomer consisted of methyl resonances at 63 and 69 cps from TMS, while these resonances for the endo isomer occurred at 62 and 70 cps from TMS. The two isomers gave the same mixture in sulfur dioxide, indicating epimerization in this solvent. The pmr data and assignment of the exo and endo alcohols and chlorides used in the cation experiments are shown in Figure 6. Careful epimerization studies on the alcohols showed the equilibrium mixture in sulfur dioxide without added catalyst at 65° C. to be 53:46 in favor of the exo alcohol. The data compare favorably with 2.6:1.0 for the exo:endo ratio in water-dioxane (10). All indications are that the ground state free energy differences between exo and endo chlorides and alcohols are small. The 1,2-dimethyl-2-norbornyl cation spectrum (Figure 7) was temperature independent from 0° C. to -105° C. At the lowest temperatures there was slight broadening ($\approx$ 4 cps) of the peak at 149 cps, but this is not large enough to be assigned to impending nonequivalence of the two methyl groups.

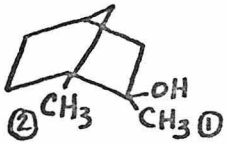
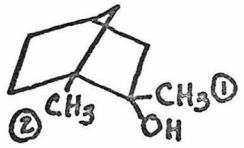
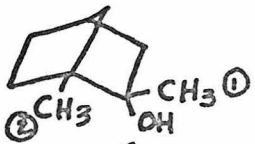
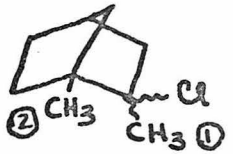
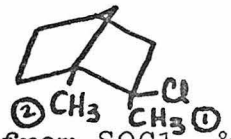
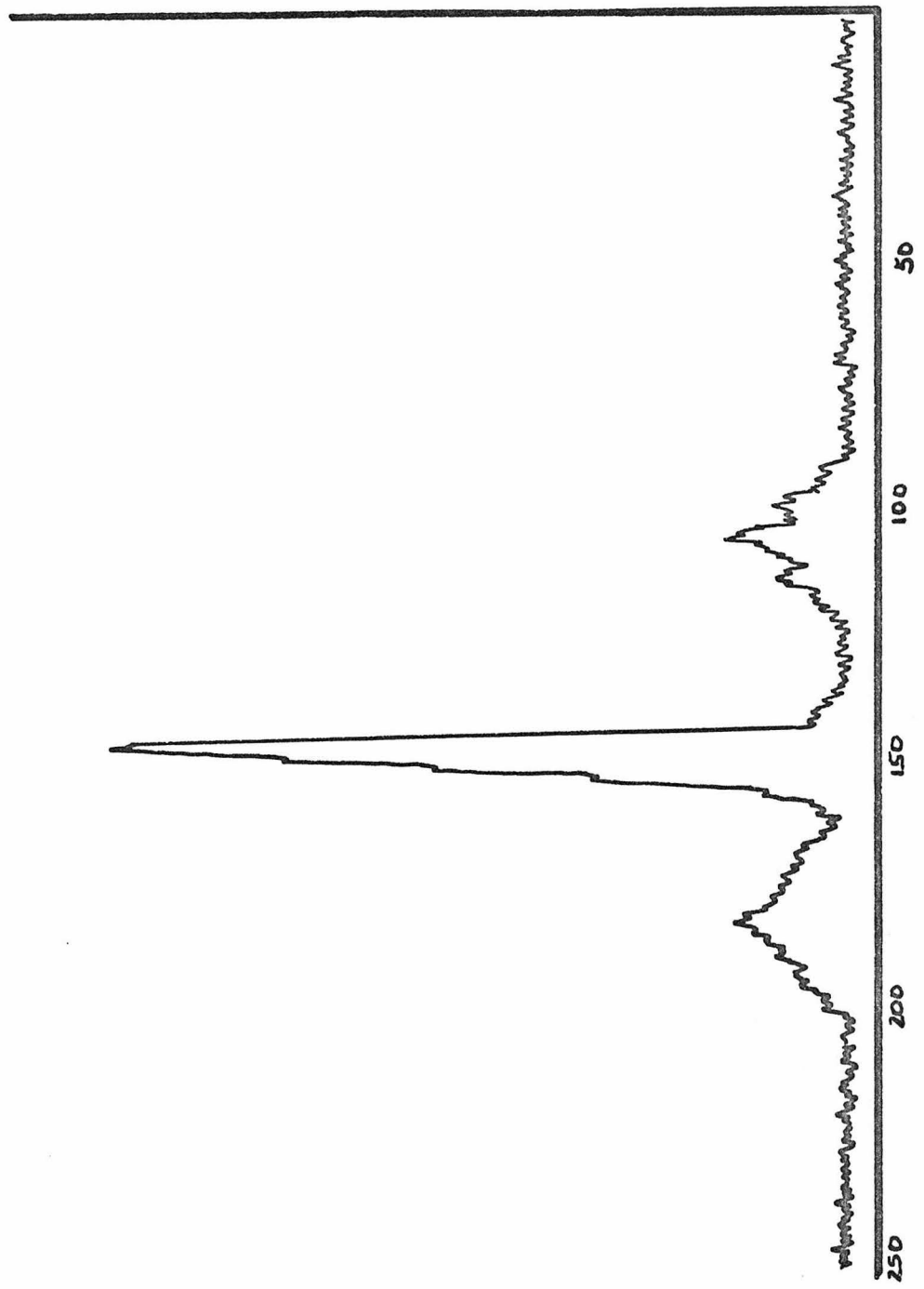
compound	solvent	$CH_3$① δ(TMS) cps	$CH_3$② δ(TMS) cps	$\delta CH_3$① - $\delta CH_3$② cps	≈% isomer
	CCl_4	69	63	6	100% <u>exo</u>
	CCl_4	70	62	8	100% <u>endo</u>
 <u>or</u> 	SO_2	33 32	22 24	11 8	≈ 30% <u>endo</u> ≈ 70% <u>exo</u>
	CCl_4	96 89	74 80	22 19	≈ 33% <u>endo</u> ≈ 67% <u>exo</u>
from HCl & alcohol	SO_2	86 82	62 55	24 17	≈ 33% <u>endo</u> ≈ 67% <u>exo</u>
 from $SOCl_2$ & alcohol	CCl_4	91	72	19	100% <u>exo</u>

Figure 6



pmr spectrum of 1,2-dimethylnorbornyl cation

Figure 7

An attempt was made to prepare the fully deuterated 1,2-dimethyl-d_6-2-norbornyl alcohol, but some of the label at the C-1 methyl group was lost during reduction of the nitrate ester of 1-methyl-2-norbornyl alcohol. Mass spectral analysis of 1-methyl-2-norcamphor indicated 1.9 hydrogens in the partially deuterated methyl group (Figure 8).

peak	intensity	specie	abundance
M-1	0.062		
M	1.000	CH_3	0.331
M+1	1.086	CH_2D	0.355
M+2	0.724	CHD_2	0.218
M+3	0.331	CD_3	0.097
M+4	0.059		
			total H 1.9

Figure 8

The pmr spectrum of the dimethyl-$d_{4.1}$-norbornyl cation showed the resonance at 149 cps to be that of the methyl groups and four other protons (Figure 9).

The cation solution was quenched with water to give a 47% yield of a compound whose pmr and ir spectra were identical with those of 1,2-dimethylnorbornyl alcohol. The pmr spectrum did not indicate any secondary alcohols. Gas-liquid partition chromatography showed the product to be a mixture of <u>exo</u> and <u>endo</u> alcohols. The percentage of <u>endo</u>

	Integrated Areas		
	100 cps	149	181
dimethyl cation	2.1 [a]	9.6 -6.0 methyl protons 3.6	3.3
dimethyl cation $CD_3\ CH_{1.9}\ D_{1.1}$	2.2 [b]	5.8 -1.9 methyl protons 3.9	2.9

[a] 16 cat scans

[b] 17 cat scans

Figure 9

alcohol varied in four experiments from 14% to 30%.

2-Methylnorbornyl cation was prepared from either 2-methyl-2-norbornyl alcohol or 2-methyl-2-chloronorbornane. The methyl resonances of the alcohols and chlorides are shown in Figure 10. The pmr spectrum of 2-methylnorbornyl cation at -67° C. is shown in Figure 11. The spectrum was temperature independent from -58 C. to -100 C. The cation generated from 2-methyl-d3-2-endo norbornyl alcohol gave the integrated results in Figure 12. The methyl group is clearly the resonance at 196 cps. When the cation is quenched with water, an alcohol is obtained whose pmr and ir spectra are the same as those of 2-methyl-2-norbornyl alcohol. Gas-liquid partition chromatography indicates that the alcohol is a mixture of 97% 2-methyl-2-norbornyl alcohol and 3% 1-methyl-2-norbornyl alcohol.

The cation spectrum shows temperature dependent changes on warming to -18° C. or -29° C. These changes do not represent thermal decomposition; on cooling to -67° C. the original spectrum is obtained. The high temperature spectrum is shown in Figure 13. The integrals for this spectrum and for 2-methyl-d3-2-norbornyl cation are shown in figure 14.

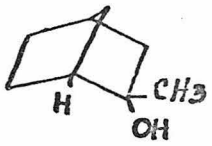
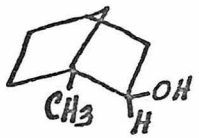
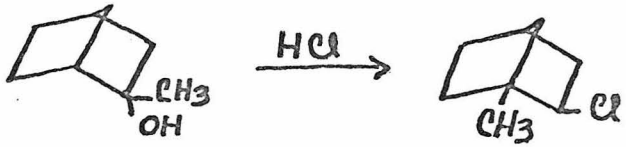
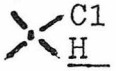
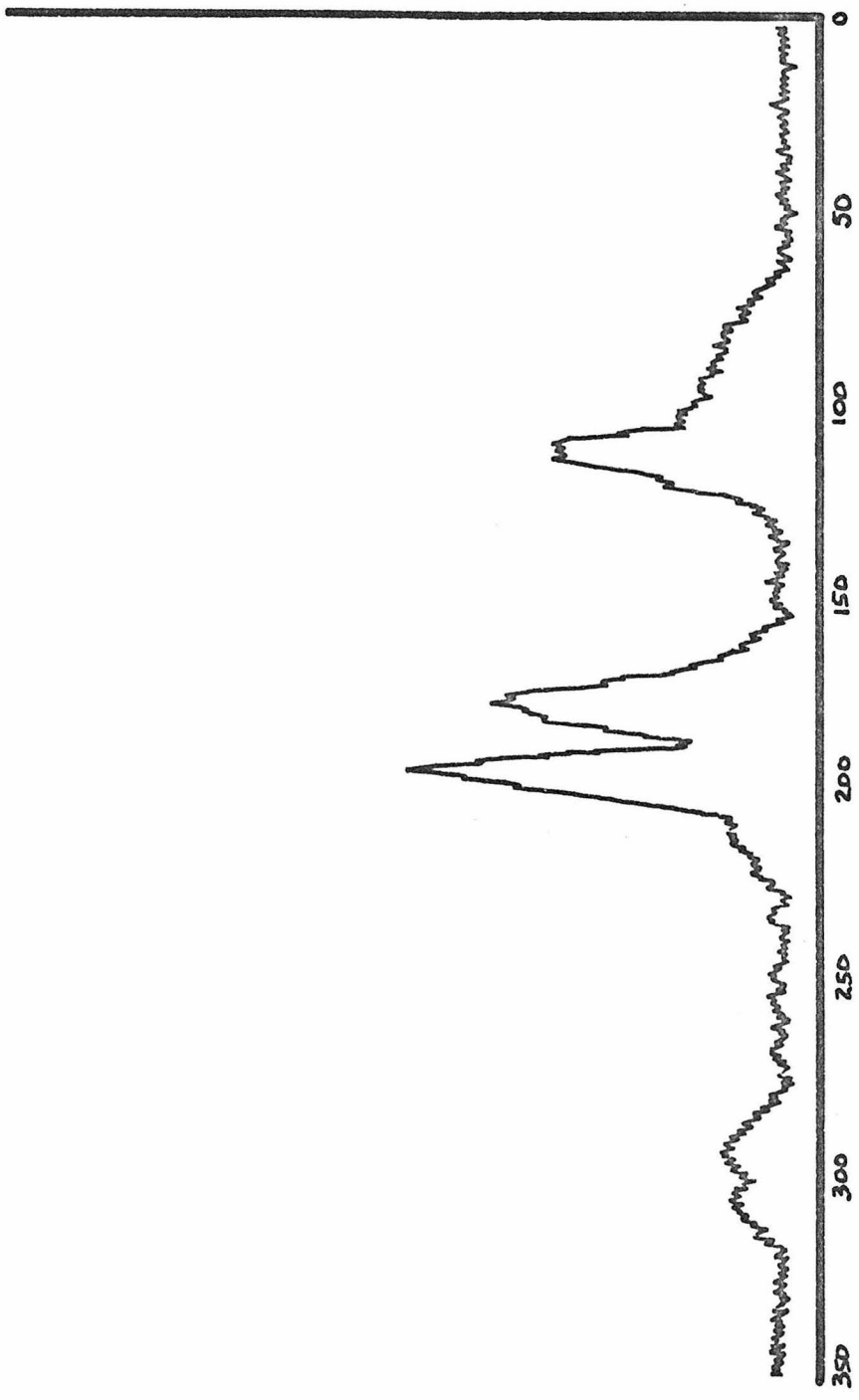
Compound	δ methyl(TMS) in CCl_4 cps	stereochemistry
	76	<u>endo</u>-Grignard
	64	<u>exo</u>
	62	multiplet 221 cps 
	98	exo

Figure 10



pmr spectrum of 2-methylnorbornyl cation (-67°C.)

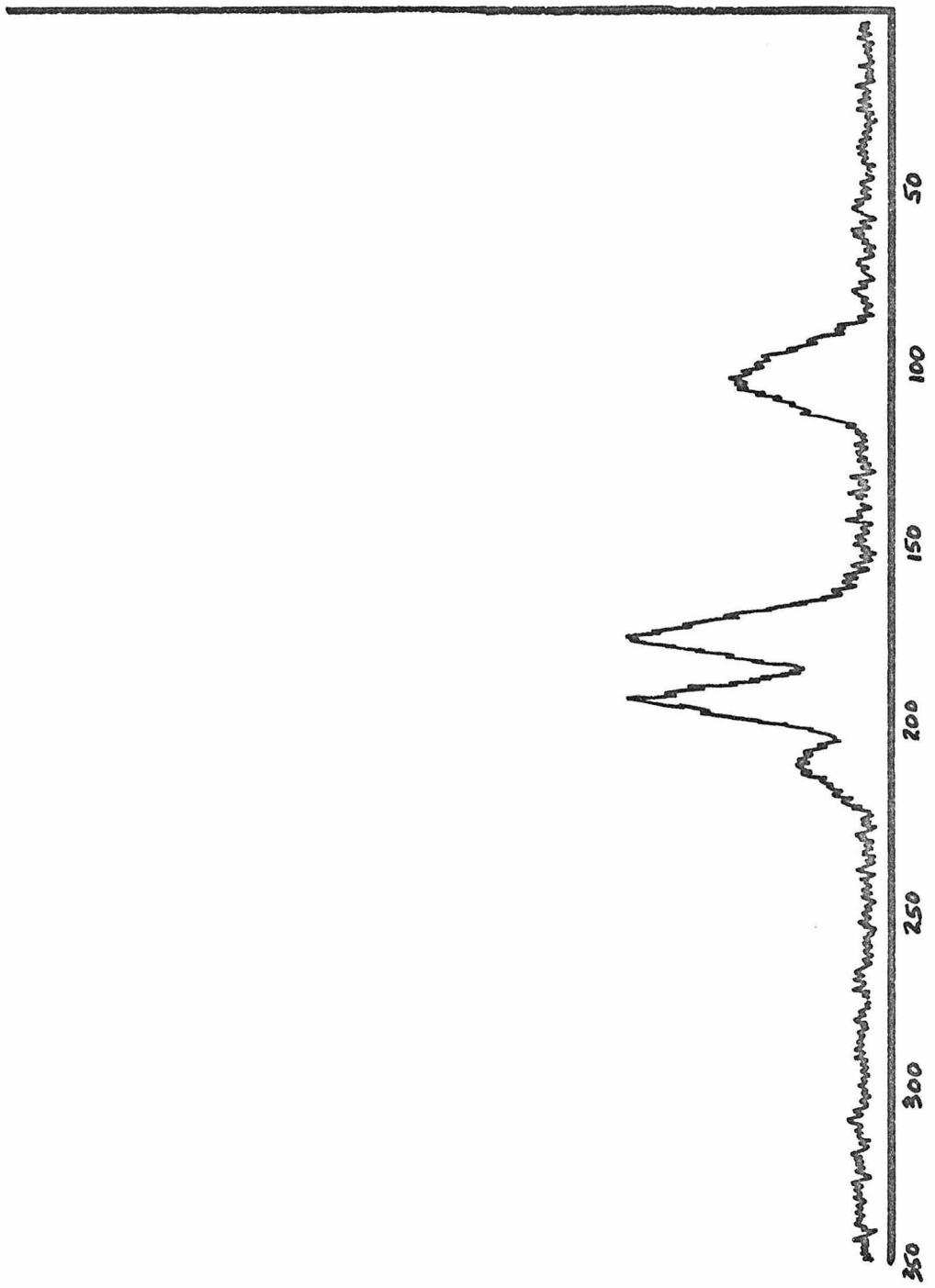
Figure 11

	Integrated Areas		
(-67°C)	299 cps	206 cps, 196 cps, 185 cps	117 & higher cps
CH_3	1.0 [a]	7.2 [a]	4.8 [a]
CD_3	0.8 [b]	0.8 [b] / 3.0 [b]	5.2 [b]

[a] 10 cat scans

[b] 36 cat scans

Figure 12



pmr spectrum of 2-methylnorbornyl cation (-18° C)

Figure 13

Integrated Areas

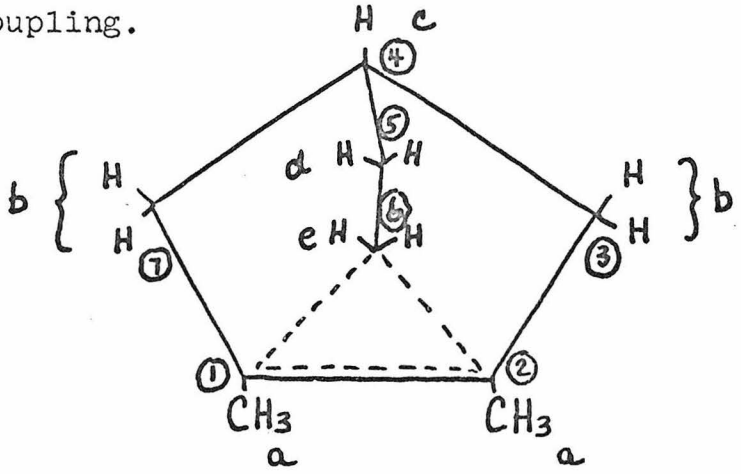
	210 cps	193 cps	180 cps	104 cps
CH_3		8.1 8.5		4.9 4.5
CH_3		6.0		4.0

Figure 14 (integrals are from single scan spectra)

The methylcyclopentyl cation pmr spectrum consists of an upfield quintet at 140 cps and a downfield multiplet. The lower part of the multiplet at 246 cps has been assigned to the methylene protons α to the methyl group at 230 cps (17). Olah did not confirm his assignment by deuterium studies, so 1-methyl-d_3-1-chlorocyclopentane was synthesized and the carbonium ion prepared. The deuteromethylcyclopentyl cation pmr spectrum consisted of two quintets: one upfield at 140 cps and a broad downfield quintet at 246 cps. Therefore, Olah's assignment of the spectrum is confirmed. The breadth of the downfield quintet compared to the upfield quintet is consistent with long range coupling between D and H through the sp^2 carbon. The long range H-H coupling constant between the methyl and methylene protons is reported by Olah as 4 cps (17).

DISCUSSION

The following assignment of the 1,2-dimethyl-2-norbornyl cation (XI) is consistent with chemical shifts, integration of the spectrum, deuteration, and observed coupling.



XI

Deuteration of the methyl groups establishes that the methyl protons, a, occur in the sharp peak at 149 cps. Integration of this peak indicates 3.6-3.9 protons in the shoulder of the methyl peak. These protons are assigned to the four methylene protons α to the positive charge. This is consistent with the relative shift of the methylene protons in other tertiary carbonium ions. These protons occur just downfield (13 cps and 20 cps) of the methyl resonance in methylcyclopentyl cation and in t-amyl cation. This leaves the protons at C-5 and C-6 as the high field and low field resonance peaks. It seems reasonable to assign the C-6 protons, e, to the low field peak because of their proximity to the positive charge. The high field triplet

and the low field broadened triplet are apparently coupled to each other $J_{H-H} \approx 6.0$ cps. This is consistent with the large coupling constant predicted for two vicinal protons with a dihedral angle $\phi = 0$ such as the protons at C-5 and C-6 (23). The total width of the overlapped pattern at 149 cps is not enough to explain coupling to either the low or high field resonances. This leaves the bridgehead proton, c, at the low field resonance and may account for the poor resolution of this signal. The bridgehead proton's resonance appears to be downfield farther than expected. However, the bridgehead proton in 1-methylnorbornane is downfield 0.7 ppm from the ring methylene protons (24). It therefore seems possible that the bridgehead proton could occur 1.3 ppm downfield from the methylene proton farthest from the positive charge.

The interesting point in the 1,2-dimethylnorbornyl cation spectrum is that the methylene protons at C-6, while not directly bonded to the carbonium ion center, are farther downfield than the methylene protons at C-3 and C-7 which are α to the positive charge.

The lack of broadening of the spectrum to -105° C. deserves more comment. Assuming that 1,6 and 3,2 hydride shifts play a small role in the observed spectrum because of the small amount of secondary cation present, the only observable rate process would be equilibration of the methyl groups by Wagner-Meerwein rearrangements. We can

estimate such a rate process from estimated shifts of the nonequivalent methyl groups using the shape function equation for intermediate rate of exchange between two

Figure 15

sites with equal populations. It would have been possible to see broadening of $2\pi\tau(\nu_A - \nu_B) = 1$ (25). The chemical shift can be estimated from the shift of the methyl group in 2-methylnorbornyl cation at 195 cps and the single methyl group in t-amyl cation at 105 cps. Thus $\nu_A - \nu_B = 90$/sec, and k_1 minimum$= 2.82 \times 10^{+2} sec^{-1}$; this corresponds to a maximum $\Delta G^{\ddagger} = 7.5$ kcal/mole. This compares with Olah's estimate of $\Delta G^{\ddagger} = 5.5$ kcal/mole for the Wagner-Meerwein rearrangement in norbornyl cation (20).

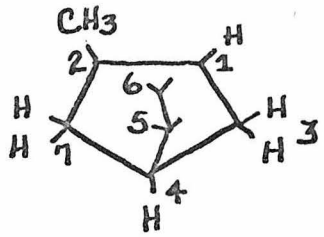
Some comparisons of the dimethylnorbornyl cation with other tertiary cations are possible. Figure 16 shows the chemical shift differences of the methyl groups in a few tertiary cations and their chlorides (i.e.chemical shifts due to ionization). The effect of charge delocalization in the last two cations in Figure 16 is striking. The dimethyl-norbornyl cation shows no observable long range coupling between the methyl group and the methylene α to the

positive charge unlike t-amyl and methylcyclopentyl cations.

cation	cation-chloride	cation	chloride
methyl cyclopentyl	134	232	98
t-amyl	142	238	96
t-butyl	138	238	100
2-methylnorbornyl	110	196	86
1,2-dimethylnorbornyl	65	149	86 exo 82 endo
2,3,3-trimethylbutyl	64	164	100

Figure 16

The pmr data are not good enough to justify an unambiguous assignment for the 2-methylnorbornyl cation. However, it is possible to make an assignment consistent with the observed spectrum. The low field peak of one proton at 300 ppm, the secondary alcohols recovered in quenching of the ion, and the value of the chemical shift difference from the chloride to the cation all indicate significant charge delocalization from the tertiary cation. We have assigned the low field single proton peak to the proton at C-1.



The ion is assigned the delocalized structure XII because the proposed Wagner-Meerwein shift which places positive charge at C-1 is still fast at the lowest temperatures studied.

The protons at C-3, being α to the positive charge, are assigned to the resonance at 180 cps. The C-4 single proton is also assigned to the 180 cps resonance by analogy to 1,2-dimethylnorbornyl and norbornyl cations, where the chemical shift of this proton is 180 and 190 cps respectively (20). The four protons at C-5 and C-7 and one of the protons at C-6 are assigned to the high field resonance at 117 cps. This leaves the other proton at C-6 at 200 cps. The location of the three methyl protons at 196 cps can be seen from the spectrum of the deuteromethylnorbornyl cation. This assignment is consistent with the spectrum and integrals at -67° C. for both the deuterated and undeuterated cation.

This assignment is also consistent with the high temperature spectra if 1,6 hydride shifts are allowed to cause fast equilibration of ions A and B (p.32). Since the tertiary ion is present in far larger concentration than the secondary, the presence of such secondary ions will facilitate proton equilibration. Their presence may also cause small downfield shifts due to a small population of secondary ions in rapid equilibrium with the tertiary ion. The Wagner-Meerwein rearrangements and 1,6 hydride shifts

between secondary cations equilibrate the hydrogens at C-6 and C-1, at C-5 and C-7, and the exo and endo hydrogens at C-3 as seen in Figure 17. This explains the sharpening of the resonance at 185 due to exchange of the exo and endo protons at C-3. It also explains the upfield shift of the proton at C-1 and the downfield shift of one of the protons at C-6. The upfield resonance at 117 cps sharpens into a symmetrical pattern because of equilibration between C-5 and C-7. The low field broad multiplet in the high temperature spectrum is assigned to the protons at C-1 and C-6 which seem to be exchanging at intermediate rate. The upfield resonance and the resonance at 185 cps sharpen substantially while that at $\approx$ 200 cps remains broad even though equilibration occurs by the same rate process because the $\tau \cdot \delta$ term in the nmr line shape equation remains larger for the protons at C-1 and C-6 (200 cps) than for the protons at C-7, C-5 and C-3. This is due to the much larger chemical shift difference between the protons at C-1 and C-6 than between the C-5 and C-7 or the C-3 endo and exo protons.

The explanation for the relatively slower 1,6 hydride shift and Wagner-Meerwein rearrangement in the 2-methylnorbornyl cation relative to that in norbornyl cation is that the lifetime for equilibration between A and B is determined by the amount of secondary cation present. This is presumed to be low in comparison to total 2-methylnorbornyl

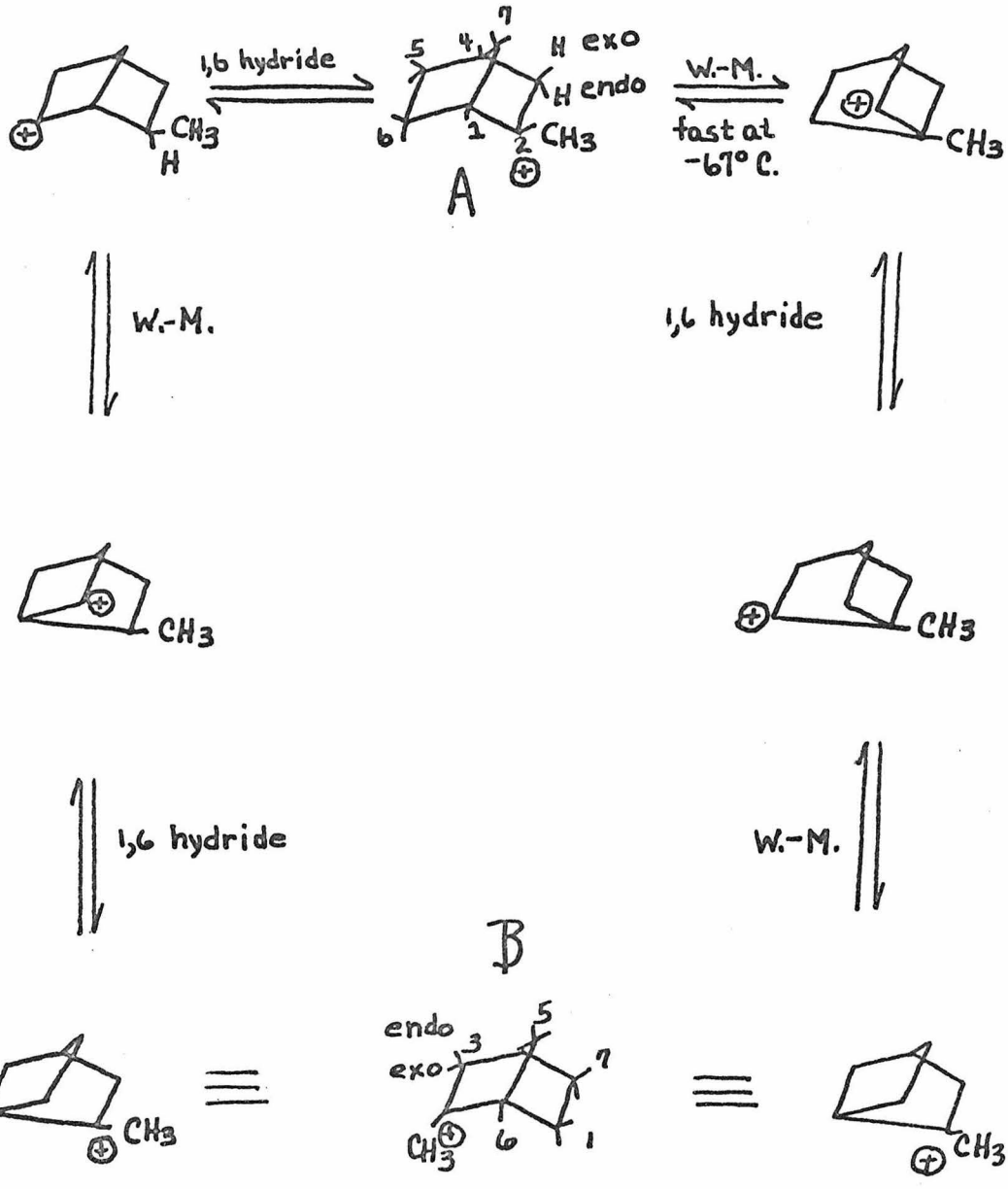

1,6 hydride
H exo
H endo
W.-M.
fast at
-67° C.
CH3
H
A
W.-M.
1,6 hydride
1,6 hydride
W.-M.
B
endo
exo
CH3
CH3
CH3
CH3

Figure 17

cation. The Wagner-Meerwein rearrangement of tertiary to secondary cation seems to be occurring even at -105° C. This can be seen in the large deshielding of the proton at C-1, indicating some positive charge at this position. If we take its normal shift as 180 cps (proton at C-4), the observed shift due to the charge at C-1 and C-2 is 120 cps. A comparison with the shift difference between the protons at C-3 and those at C-5 and C-7 in 2-methyl-norbornyl cation indicates that a deshielding of 80-90 cps is reasonable for protons α to the positive charge. This indicates that the resonance for the proton at C-1 is about 30 cps farther down field than expected. In light of the secondary products isolated on quenching and the small shift in the methyl resonance between 2-methylnorbornyl cation and chloride (Figure 16), it seems possible that this extra deshielding at C-1 is a result of charge delocalization to the 1-methylnorbornyl cation formed by a rapid Wagner-Meerwein rearrangement.

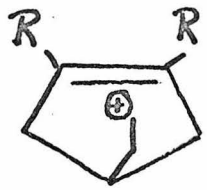
These spectral observations are not inconsistent with nonclassical formulation for 1,2-dimethylnorbornyl and 2-methylnorbornyl cations. Furthermore, the secondary methylnorbornyl cations seem to be unusually stable with respect to the tertiary 2-methylnorbornyl cation. This extra stability is consistent with the nonclassical formulation for secondary norbornyl cations.

The C-6 protons of 1,2-dimethylnorbornyl cation are deshielded 80 cps with respect to the C-5 protons. In 2-methylnorbornyl cation one of the C-6 protons is deshielded by ≈ 100 cps with respect to the other C-6 proton and the protons at C-5. Several explanations can account for this deshielding. A 1,6 hydride shift would account for deshielding of the C-6 exo proton in 2-methylnorbornyl cation and of both equivalent protons in the 1,2-dimethylnorbornyl cation. This cannot account for the total 80 cps or 100 cps shift observed, however. If we take the maximum deshielding of the proton at C-1 due to Wagner-Meerwein rearrangement of 2-methylnorbornyl cation as 30 cps (p.33), then the C-6 proton should be deshielded by about 30 cps due to a 1,6 hydride shift. This expectation arises because the stability of the secondary cations formed by a 1,6 hydride shift or Wagner-Meerwein rearrangement should be nearly the same. Another indication that 1,6 hydride shifts are unimportant in 1,2-dimethylnorbornyl cation is the equality of the chemical shifts due to ionization for this cation and for the 2,3,3-trimethyl-2-butyl cation (Figure 16). Since charge delocalization by hydride shift is highly unlikely in 2,3,3-trimethyl-2-butyl cation, this observation indicates the absence of such delocalization in 1,2-dimethylnorbornyl cation. Another effect that could account for the stereospecific deshielding is overlap between the empty p orbital and the backside lobe of the sp^3

C-H orbital for the exo proton (Figure 13) (19). This would account for some deshielding of the C-6 exo proton

XIII

in 2-methylnorbornyl cation and both C-6 protons in the 1,2-dimethylnorbornyl cation. Another possibility for charge delocalization is through resonance form XIV which has been proposed for nonclassical norbornyl cations.



XIV

This type of delocalization would deshield both protons at C-6. Finally, a simple electric field effect on the C-H chemical shift due to a positive charge in the molecule could cause the deshielding.

The equations used for relating chemical shift of a proton to the electric field due to excess charge is

$$\Delta\sigma = - aE_z - bE^2$$

where E_z is the component of the electric field along the C-H bond. A more convenient form of this equation is

$$\Delta\sigma = 12.5 \times 10^{-6} \sum_i \left[(\Delta q_i \cos \theta_i)/R_i^2\right] - 17.0 \times 10^{-6} \left(\sum_i \Delta q_i/R_i^2\right)^2$$

where R_i is the distance from the charge Δq_i to the C-H bond and θ_i is the angle between the electric field vector and the C-H bond (27). For these calculations θ_i and R_i were evaluated from molecular models for the classical equilibrating 1,2-dimethylnorbornyl cation and the non-classical cation where one-half the positive charge is at C-1 and C-2. The bond distance from C-1 and C-2 to C-6 for the nonclassical case was taken as the average of the C-H bond distance from C-6 to C-2 and the nonbonded distance from C-6 to C-1. The effect of the counter ion was ignored in these calculations. The results of the calculations for 1,2-dimethylnorbornyl cation are shown in Figure 18.

Chemical Shift Difference ppm	classical equilibrating	non-classical	observed
H_6-H_5	- 0.07	- 1.14	- 1.3
H_6-H_4	0.76	0.01	0.06
H_6-$H_{3,7}$ exo	1.04	0.40	- 0.50
H_6-$H_{3,7}$ endo	1.38	0.15	- 0.50

Figure 18

The nonclassical model seems to predict the downfield shift of the protons at C-6 while the classical model does not. The calculation does not account for the relative

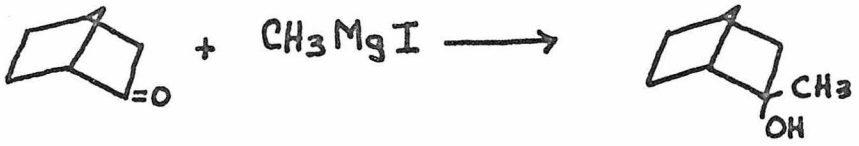
position of the C-6 proton resonance to that of the protons α to the positive charge. A small amount of positive charge character at C-6 would, however, move these C-6 protons downfield farther. A suggestion for determining whether part of the deshielding is due to charge delocalization is discussed in the propositions.

The unexpected deshielding of the C-6 protons in 1,2-dimethylnorbornyl cation may be explained in two ways. It may be the result of the electric field associated with the charge distribution in the nonclassical cation plus any charge delocalization to C-6. The other explanation is that the cation is classical, and deshielding occurs by overlap of the back lobe of the C-H orbital with the empty cation p orbital. Models indicate that the 1,2-dimethyl-norbornyl cation is not nearly as favorable for such overlap as is admantyl cation where this effect is claimed to cause a deshielding of 0.92 ppm for the γ protons relative to the β protons. Therefore, we favor the first explanation.

EXPERIMENTAL

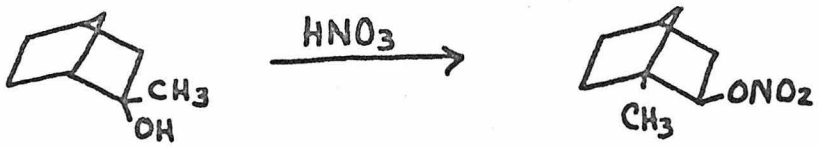
A. Syntheses

1) 2-Methyl-2-endo-norbornyl alcohol



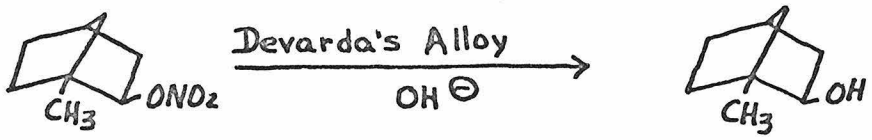
Methyl magnesium iodide (0.557 moles) was added with stirring under nitrogen to 40.8 g (0.372 moles) norcamphor (Aldrich). The alcohol product was isolated and distilled to give 39.6 g (0.314 moles, 84%) 2-methyl-2-endo-norbornyl alcohol (21).

2) 1-Methyl-2-exo-norbornyl nitrate

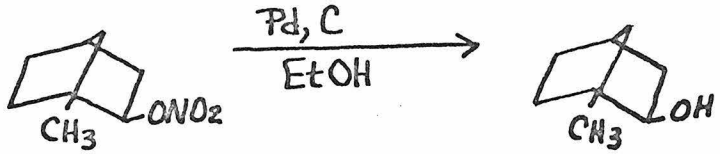


2-Methyl-2-endo-norbornyl alcohol (67 g, 0.532 moles) was added to 370 ml concentrated nitric acid (new bottle, N_2O_4 free). This mixture was stirred at room temperature for 10 hours. It was then poured into 1 liter of ice water, and the organic product was extracted with ligroin (30-60). The ligroin was washed with sodium bicarbonate and dried with magnesium sulfate. The crude yield of nitrate ester was 84 g (0.492 moles, 92%) (21).

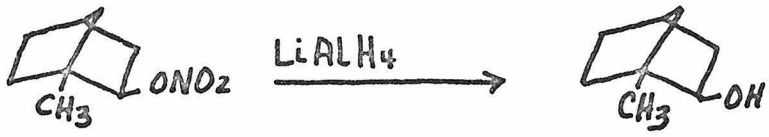
3) 1-Methyl-2-exo-norbornyl alcohol

(a) 

The nitrate ester (84 g, 0.492 moles) was dissolved in 1 liter 85% ethanol. To this mixture, portions of 50 g Devarda's alloy and 46 g potassium hydroxide in 46 ml water, were added at 6, 10, 25 and 53 hr. During addition the solution was cooled to keep the stirred mixture at room temperature. The ethanol was removed, and the product steam-distilled to give 35 g (0.278 moles, 57%) 1-methyl-2-exo-norbornyl alcohol: bp 83-88 (20 mm) (21).

(b) 

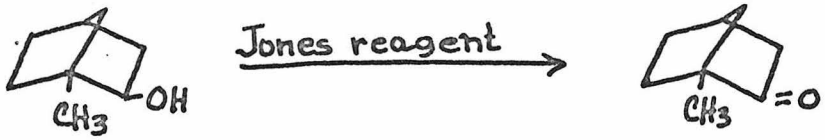
The nitrate ester (8.0 g, 0.047 moles) was dissolved in ethanol, and this solution was placed in a Parr reducing apparatus. Catalytic reduction was carried out at 30 psi with 20 g 5% Pd on charcoal. The reduction was complete in 2 hr and gave 3.2 g (0.025 moles, 54%) alcohol.

(c) 

The nitrate ester (12.4 g, 0.073 moles) was refluxed overnight with 9.1 g (0.240 moles) lithium aluminum hydride

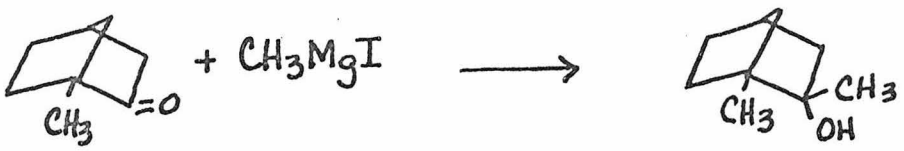
in ether. The excess lithium aluminum hydride was destroyed with ethyl acetate, and the reaction mixture was poured into 200 ml 3 N hydrochloric acid. The aqueous layer was extracted with ether. The ether layer contained 7.4 g (0.058 moles, 81%) crude alcohol product.

4) 1-Methylnorcamphor



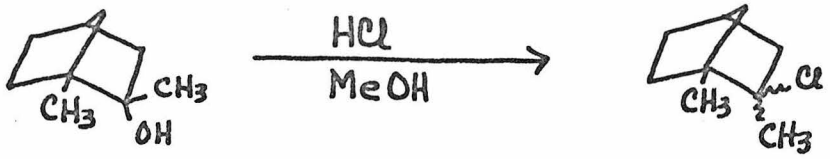
1-Methyl-2-exo-norbornyl alcohol (35 g, 0.278 moles) was dissolved in 78 ml acetone, and Jones reagent [27 g chromium trioxide (0.270 moles), 18 ml water, 23 ml sulfuric acid] was added to the alcohol during the course of one hour. During addition of the reagent, the solution was kept at 0° C. The ice bath was removed, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was quenched with 750 ml water, and the product was extracted with ligroin (30-60). The ligroin solution was washed with sodium bicarbonate and dried. The product, 1-methylnorcamphor: bp 73-80 (19-21 mm), weighed 18.5 g (0.149 moles, 54%).

5) 1,2-dimethyl-2-endo-norbornyl alcohol



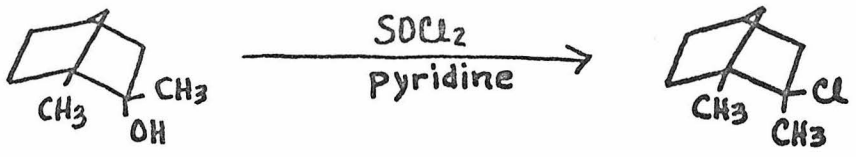
The ketone (18.5 g, 0.149 moles) was treated with methyl magnesium iodide as before to give 20.7 g (0.148 moles, 99%) 1,2-dimethyl-2-endo-norbornyl alcohol (22).

6) 1,2-Dimethyl-2-chloronorbornane

(a) 

1,2-Dimethyl-2-endo-norbornyl alcohol (9.7 g, 0.069 moles) was dissolved in 6 ml methanol. This solution was stirred overnight with 80 ml concentrated hydrochloric acid. The mixture was extracted with ligroin (30-60), and the chloride was isolated and sublimed to give 7.5 g (0.047 moles, 68%) (22).

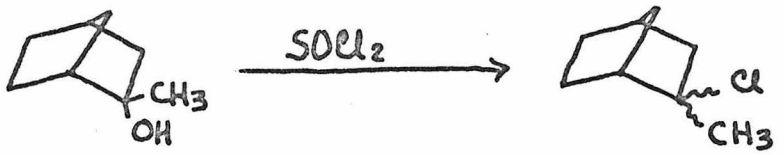
The chloride was dissolved in 40-60% ethanol, and 10 ml 0.0883 N sodium hydroxide was added. The mixture was allowed to stand overnight and was back-titrated with 0.0530 N potassium acid phthalate. 1,2-Dimethyl-2-chloro-norbornane showed 98% purity for a tertiary chloride with molecular weight 158.5.

(b) 

1,2-Dimethyl-2-endo-norbornyl alcohol (1.40 g, 0.010 moles) was dissolved in 15 ml dry ether. To this solution 0.790 g pyridine (0.010 moles) and 0.595 g (0.005 moles)

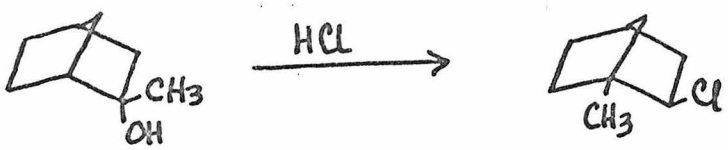
thionyl chloride were added at -78° C. The solution was warmed to room temperature, and the pyridine hydrochloride was removed by filtration. The ether was removed with a rotary evaporator, and more thionyl chloride (0.595 g, 0.005 moles) was added at room temperature. This mixture was stirred at room temperature overnight. The product was extracted with ligroin, dried, and the ligroin removed to give 1,2-dimethyl-2-exo-norbornyl chloride.

7) 2-Methyl-2-chloronorbornane



2-Methyl-2-endo-norbornyl alcohol (7.18 g, 0.057 moles) was treated with pyridine-thionyl chloride as before. The product was 6.65 g (0.046 moles, 80%) 2-methyl-2-chloronorbornane. Titration as before showed the product to be 97% tertiary chloride of molecular weight 144.5.

8) 1-Methyl-2-chloronorbornane

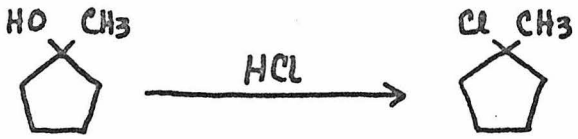


2-Methyl-2-endo-norbornyl alcohol, when treated with hydrochloric acid as before, gave predominantly (≈ 80%) 1-methyl-2-chloronorbornane.

9) 1,2-Dimethyl-2-exo-norbornyl alcohol

1,2-Dimethyl-2-chloronorbornane (1.7 g, 0.011 moles) was dissolved in 5.2 ml acetone, 1.7 ml ether, and 3 ml water. To the solution 12.1 ml 1 N sodium hydroxide was added. The solution was stirred overnight and extracted with ligroin (30-60). The product was chromatographed on alumina to give 432 mg (0.003 moles, 29%) 1,2-dimethyl-2-exo-norbornyl alcohol (22).

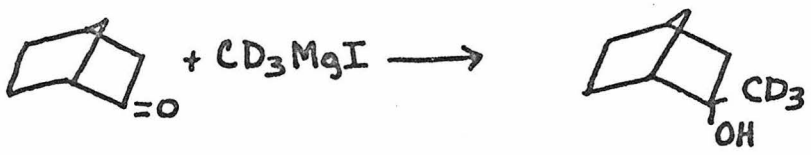
10) 1-Methyl-1-chlorocyclopentane



Methylcyclopentyl alcohol (9.0 g, 0.090 moles, Aldrich) was placed in a test tube, and dry hydrochloric acid was bubbled through the alcohol for 30 minutes. After initial addition of hydrochloric acid, the reaction vessel was cooled in an ice bath. The product was extracted with ether, and this ether solution was washed with sodium bicarbonate and dried. The chloride: bp 105-115, was distilled to give 5.0 g (0.042 moles, 47%) 1-methyl-1-chlorocyclopentane (28). Titration as before indicated the product to be 98% tertiary chloride of molecular weight 118.5.

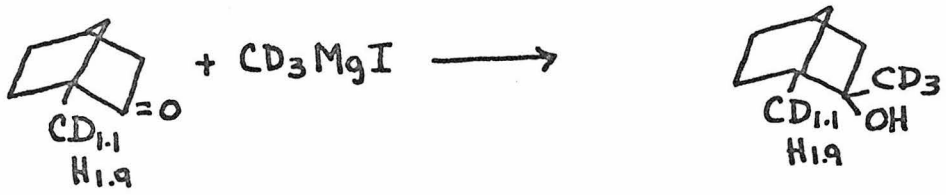
B. Deuterated Compounds

1) 2-Methyl-d_3-2-<u>endo</u>-norbornyl alcohol



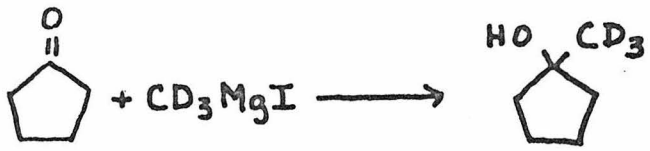
Deuteromethyl magnesium iodide (0.012 moles) was prepared from 16.8 g (0.012 moles) deuteromethyl iodide (99% d_3, Merck of Canada) and 2.84 g (0.012 moles) magnesium. Norcamphor (11.87 g, 0.011 moles, Aldrich) was treated as before with the Grignard reagent. The product was isolated as 8.9 g (0.007 moles, 64%) 2-methyl-d_3-2-<u>endo</u>-norbornyl alcohol: bp 83 (20 mm).

2) 1,2-Dimethyl-$d_{4.1}$-2-<u>endo</u>-norbornyl alcohol



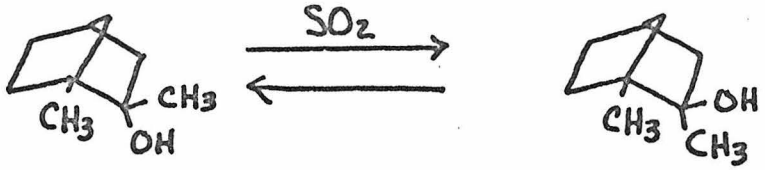
1-Methyl-$d_{1.1}$-2-norbornyl ketone (3.0 g, 0.024 moles) in 10 ml ether was treated with Grignard reagent prepared from 3.85 g (0.029 moles) deuteromethyl iodide and 647 mg (0.027 moles) magnesium. The product was isolated and chromatographed on alumina to give 900 mg (0.006 moles, 26%) 1,2-dimethyl-$d_{4.1}$-2-<u>endo</u>-norbornyl alcohol.

3) 1-Methyl-d_3-cyclopentyl alcohol



Cyclopentanone (bp 30°;Matheson, Coleman, Bell) was treated with 10% excess deuteromethyl magnesium iodide as before. The product was 300 mg deuteromethylcyclopentyl alcohol.

C. Epimerization Study



1,2-Dimethyl-2-<u>exo</u>-norbornyl alcohol (14.7 mg) and 1,2-dimethyl-2-<u>endo</u>-norbornyl alcohol were dissolved in 2.5 ml sulfur dioxide. The solutions were sealed in glass tubes and heated to 60-65° C. Tubes were opened and quenched in cold saturated sodium bicarbonate solution. The alcohols were extracted with ether and analyzed by gas-liquid partition chromatography. The column used in analysis was 12 feet of 10% carbowax 20M on chromasorb G. The epimerization was carried on until there was no change in the <u>exo</u>:<u>endo</u> ratio. The results were as follows:

starting alcohol	% exo	% endo
from endo	53	47
from exo	52	48
from endo	55	45
from exo	54	46
average	54	46

$\Delta G_{eq} = 92.4$ cal/mole

Figure 19

D. Cation Formation

Cations were produced from either alcohol (exo or endo) or chlorides. A typical preparation from an alcohol is described. 1,2-Dimethyl-2-endo-norbornyl alcohol (227 mg) was dissolved in 1.7 ml sulfurylchlorofluoride (Matheson, Coleman, Bell) at -78° C. The alcohol was dissolved by warming, and the solution was cooled to -78° C. Fluorosulfonic acid (360 µl, K. & K., redistilled) and antimony pentafluoride (450 µl, Allied Chemical, distilled at atmospheric pressure under argon in a quartz distilling apparatus) were placed in the reaction vessel (Figure 20). Sulfur dioxide was condensed in the reaction vessel until the antimony pentafluoride-sulfur dioxide complex dissolved. The alcohol dissolved in the sulfurylchlorofluoride was removed and transferred to the reaction vessel in a 0.5 ml glass syringe. The syringe was fitted with a small gauge #20 needle and was precooled in liquid nitrogen. Stirring

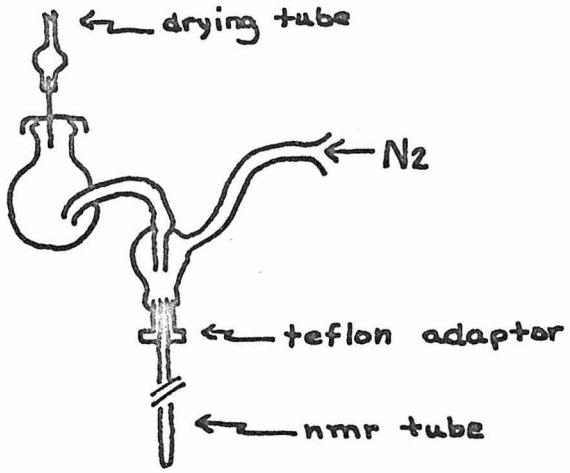


Figure 20

was provided by bubbling nitrogen through the sulfur dioxide solution of acids. The addition of alcohol was carried out slowly with vigorous stirring. The entire reaction vessel and nmr tube were immersed in a -78° C. bath during cation preparation. The cation was sucked into the nmr tube; the tube was removed and capped or sealed. A TMS capillary tube was added to each tube as a pmr reference. All spectra were taken on the Varian A56-60 spectrometer at low temperature. Many of the spectra were accumulated on a time-averaging device, CAT, using 1024 memory cells to accumulate the spectra.

All cation quenching experiments were carried out by pouring the cation into ice water, extracting with ether, and washing the ether layer with sodium bicarbonate. These

quenched solutions were analyzed by gas-liquid partition chromatography on a carbowax column as previously described. The pmr and ir spectra of the products were also recorded.

INTRODUCTION

A recent article has reported the exchange between trityl halides and trityl carbonium ions as observed by pmr (29). By studying the concentration dependence of exchange induced line broadening, the authors determined that the reaction is an SN_1 process (Figure 21). The

$$Ar_3CCl \rightleftharpoons Ar_3C^+Cl^-$$

$$Ar_3C^+Cl^- + Ar_3^oC^+Y^- \rightleftharpoons Ar_3C^+Y^- + Ar_3^oC^+Cl^-$$

Figure 21

authors extended their studies to give relative cation stabilities by carrying out exchange reactions between two cations (Figure 22). By integrating the signals in the

$$R^+ Y^- + R_oX \overset{Keq}{\rightleftharpoons} RX + R_o^+ Y^-$$

Figure 22

slow exchange case or observing the average signal of a sharp methyl or methoxy group, it proved possible to evaluate Keq (30). The technique has been used only for those compounds whose cations have been crystalized.

Several other methods of evaluating relative cation stabilities have been investigated. One of these is the study of the carbinol-carbonium ion equilibrium in strongly acidic solution (usually sulfuric acid). The resulting

carbonium ion concentration is measured by ultraviolet spectroscopy (31). This uv method is limited to those aromatic cations which are sufficiently ionized in sulfuric acid. This method also relies on the validity of the H_R acidity function.

More recently relative cation stabilities have been studied by comparing E_o measurements for the half cell shown in Figure 23. The comparison of the half cell reaction

$$R^+ + e \rightleftharpoons \tfrac{1}{2}\ R\text{-}R$$

Figure 23

for two cations gives their relative stability. These stability differences are close to those measured by the carbinol-carbonium ion equilibrium in strong acid (32). Again this method requires an easily prepared cation and has been used only for trityl cations.

The heats of formation (calorimetric) of several carbonium ions have been measured in antimony pentafluoride-fluorosulfonic acid mixtures. Two aliphatic compounds have been studied in this way. Cyclohexene and methylcyclopentene both produce methylcyclopentyl cation with heats of formation $H_{obsd} = -16.8$ and -18.3 kcal/mole, respectively. The difference of 1.5 kcal/mole corresponds to the difference of 1.4 kcal/mole in the heats of formation of the alkenes (33).

It is our intention to extend some of these cation

stability measurements to aliphatic cations in sulfur dioxide solutions of antimony pentafluoride. We feel that such relative stability measurements will have bearing on the nonclassical formulation for certain aliphatic cations.

RESULTS

Several cation-chloride mixtures were studied in solutions containing less than one equivalent of antimony pentafluoride. We needed to know first if the cation-chloride exchange was fast or slow on the nmr time scale and second if the reaction of a tertiary chloride with antimony pentafluoride was quantitative. The most carefully studied cation was t-butyl.

A saturated solution of antimony pentafluoride in sulfur dioxide was prepared, and 0.5 ml aliquots were withdrawn in a cold syringe fitted with a teflon needle. Each aliquot was sealed in a glass tube and kept in a freezer. These aliquots were then titrated with t-butyl chloride by adding weighed amounts of the chloride and observing the average chloride-cation resonance (Figure 24).

	mg t-BuCl	chem shift (TMS)	mmoles t-BuCl	fraction cation $\frac{\Delta obsd - \Delta cl}{\Delta cat. - \Delta cl}$
	-	238 cps	-	100%
1)	33.2	242	0.358	100%
2)	51.6	148	0.557	35%
3)	52.8	231	0.570	96%
4)	64.2	194	0.692	69%
5)	66.1	140	0.714	29%
6)	75.4	154	0.814	40%
7)	75.4	159	0.814	43%
8)	76.3	167	0.824	46%
9)	101.5	145	1.095	33%
10)	120.9	137	1.302	28%
11)	152.7	115	1.648	11%
12)	250.8	105	2.705	4%
	-	100 cps	-	0%

Figure 24

It can be seen from Figure 24 that the results are only semi-quantitative, probably because of the difficulty of keeping water out of the antimony pentafluoride solutions. It is felt that it is still possible to get a reasonable estimate of Keq and the average concentration of the acid solutions. A graph of % cation against chloride concentration is shown in Figure 25. The general trend is toward lower shifts at larger t-butyl chloride concentrations. To simultaneously determine Keq and the acid concentration the following model was chosen.

$$\text{chloride} + SbF_5 \underset{}{\overset{Keq}{\rightleftharpoons}} \text{cation}^+ + SbF_5Cl^-$$

$$\Delta = \text{fraction cation} = \frac{\delta \text{obs} - \delta Cl}{\delta \text{cat.} - \delta Cl}$$

X = mmoles t-BuCl

HA = original SbF_5 - mmoles

ΔX = cation - mmoles

$$Keq = \frac{(\text{cation})^+ \cdot (SbF_5\ Cl^-)}{(\text{chloride}) \cdot (SbF_5)}$$

$$Keq = \frac{(\Delta X)^2}{(X - \Delta X)(HA - \Delta X)}$$

$$Keq = \frac{(\Delta X)^2}{HAX - HA\,\Delta X - X\,\Delta X + (\Delta X)^2}$$

$$Keq = \frac{1}{\frac{HA}{\Delta^2 X} - \frac{HA}{\Delta X} - \frac{1}{\Delta} + 1}$$

$$\frac{1}{Keq} = HA\left(\frac{1}{\Delta^2 X} - \frac{1}{\Delta X}\right) + \left(1 - \frac{1}{\Delta}\right)$$

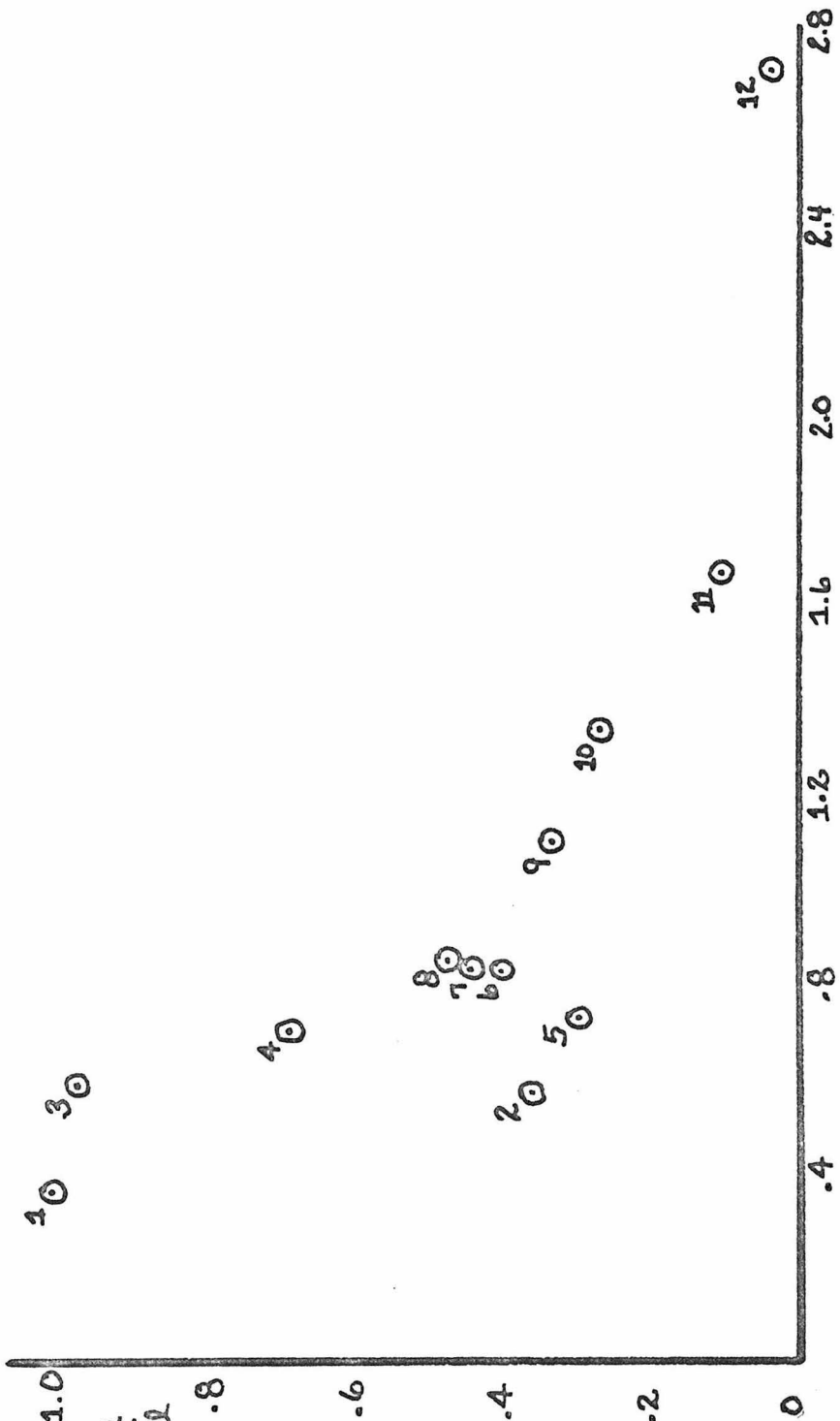

1.0
.8
.6
.4
.2
0
$\frac{\Delta_{obsd} - \Delta_{cat.}}{\Delta_{cat.} - \Delta_{cat.}}$
.4
.8
1.2
1.6
2.0
2.4
2.8
mmoles t-Bu chloride
1
2
3
4
5
6
7
8
9
10
11
12

Figure 25

$$\frac{1}{Keq} = \frac{HA}{\Delta X}\left(\frac{1}{\Delta} - 1\right) + \left(1 - \frac{1}{\Delta}\right)$$

A plot of 1/Keq against HA will be a straight line for each value of Δ and X. The intersection of all these lines will give the values of 1/Keq and HA. The lines are constructed from the values of Δ and X at the intercepts.

for the $1/Keq = 0$ intercept

$$HA = \Delta X$$

for the $HA = 0$ intercept

$$1/Keq = 1 - 1/\Delta$$

The evaluation of these intercepts is shown in Figure 26.

	Δ	X	$\frac{1}{\Delta}$	ΔX	$1 - \frac{1}{\Delta}$
1)	1.03	0.358	0.97	0.369	0.03
2)	0.35	0.557	2.86	0.195	-1.86
3)	0.96	0.570	1.04	0.548	-0.04
4)	0.69	0.692	1.45	0.477	-0.45
5)	0.29	0.714	3.45	0.207	-2.45
6)	0.40	0.814	2.50	0.325	-1.50
7)	0.43	0.814	2.32	0.350	-1.32
8)	0.49	0.824	2.17	0.403	-1.17
9)	0.33	1.095	3.03	0.362	-2.03
10)	0.28	1.302	3.57	0.370	-2.57
11)	0.11	1.648	9.09	0.180	-8.09
12)	0.04	2.708	25.0	0.110	-24.0

Figure 26

All the lines on the graph should intersect at one common point (Figure 27). That they do not is a consequence of varying acid concentrations. Most of the points of intersection do fall in the area marked with a circle in Figure 27. We feel this is consistent with the qualitative observations that Keq is large (i.e. almost

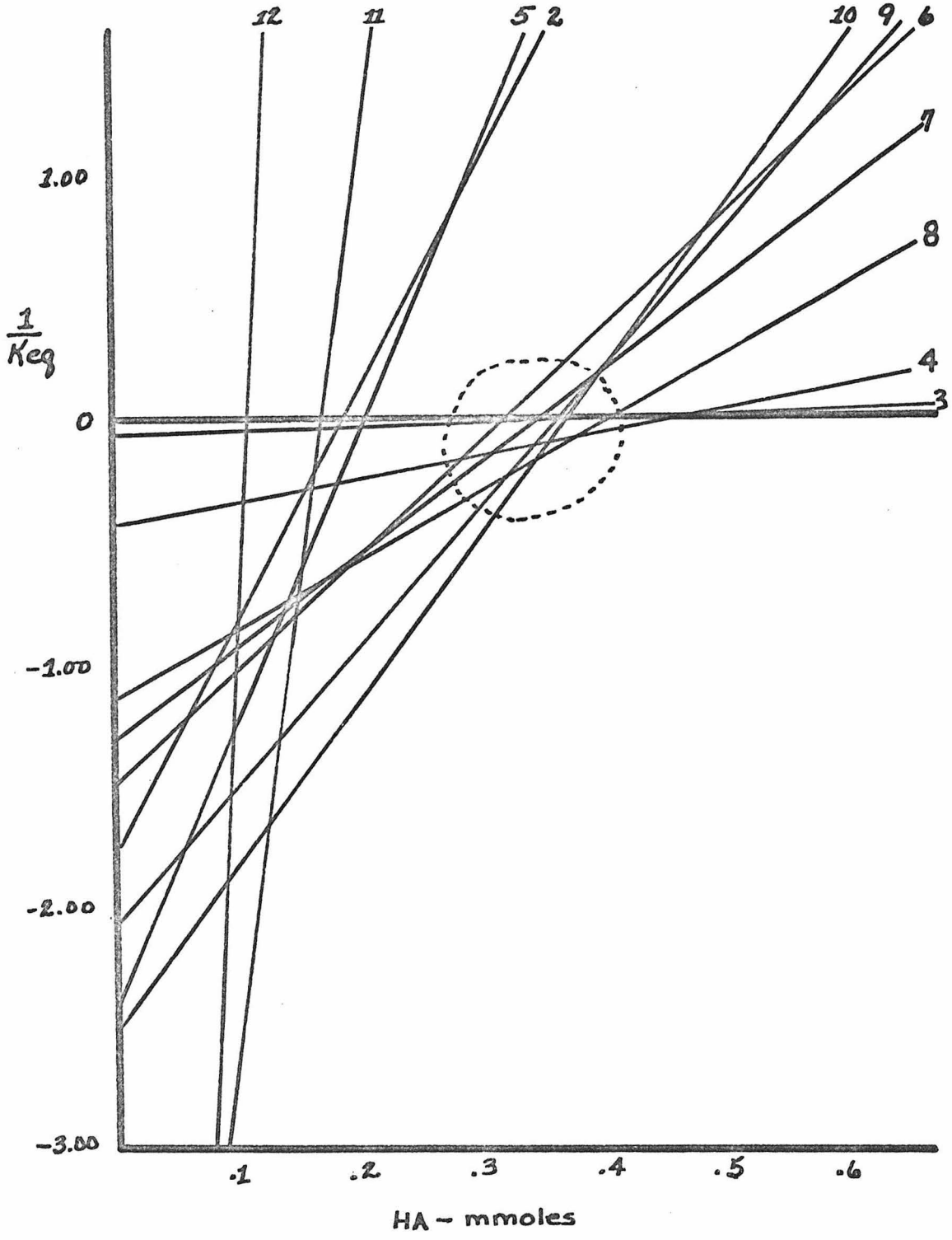


Figure 27

quantitative reaction of the antimony pentafluoride). The acid concentrations seem to fall between 0.3 and 0.5 mmoles per half-milliliter tube. We feel points which represent large amounts of t-butyl chloride do not converge near the others because the large amounts of chloride used change the character of the solvent. If we now choose the points which do seem to come close to convergence (i.e. all but 2, 5, 11, and 12) and impose the condition $1/Keq \approx 0$,

$$HA = \Delta X$$

$$X = \frac{HA}{\Delta}$$

Therefore, a plot of $\frac{1}{\Delta}$ vs X should be a straight line of slope HA. The least squares plot shown in Figure 28 gives $HA = 0.297 \pm 0.044$. The plot shows straight line behavior (variance 0.0759) indicating that our model with $\frac{1}{Keq} \approx 0$ is not too far afield. Solutions of t-butyl chloride and t-butyl cation gave mixtures of t-butyl chloride and t-butyl alcohol when quenched with water.

Other cation-chloride solutions were observed in less than one equivalent of antimony pentafluoride to see if they were stable. These fell into two groups at -78° C; those that showed fast exchange (averaged resonances) and those which showed slow chloride cation exchange.

t-Amyl cation (XIII) in less than one equivalent of acid showed fast exchange. The results of the experiments are shown in Figure 29. The acid concentration was

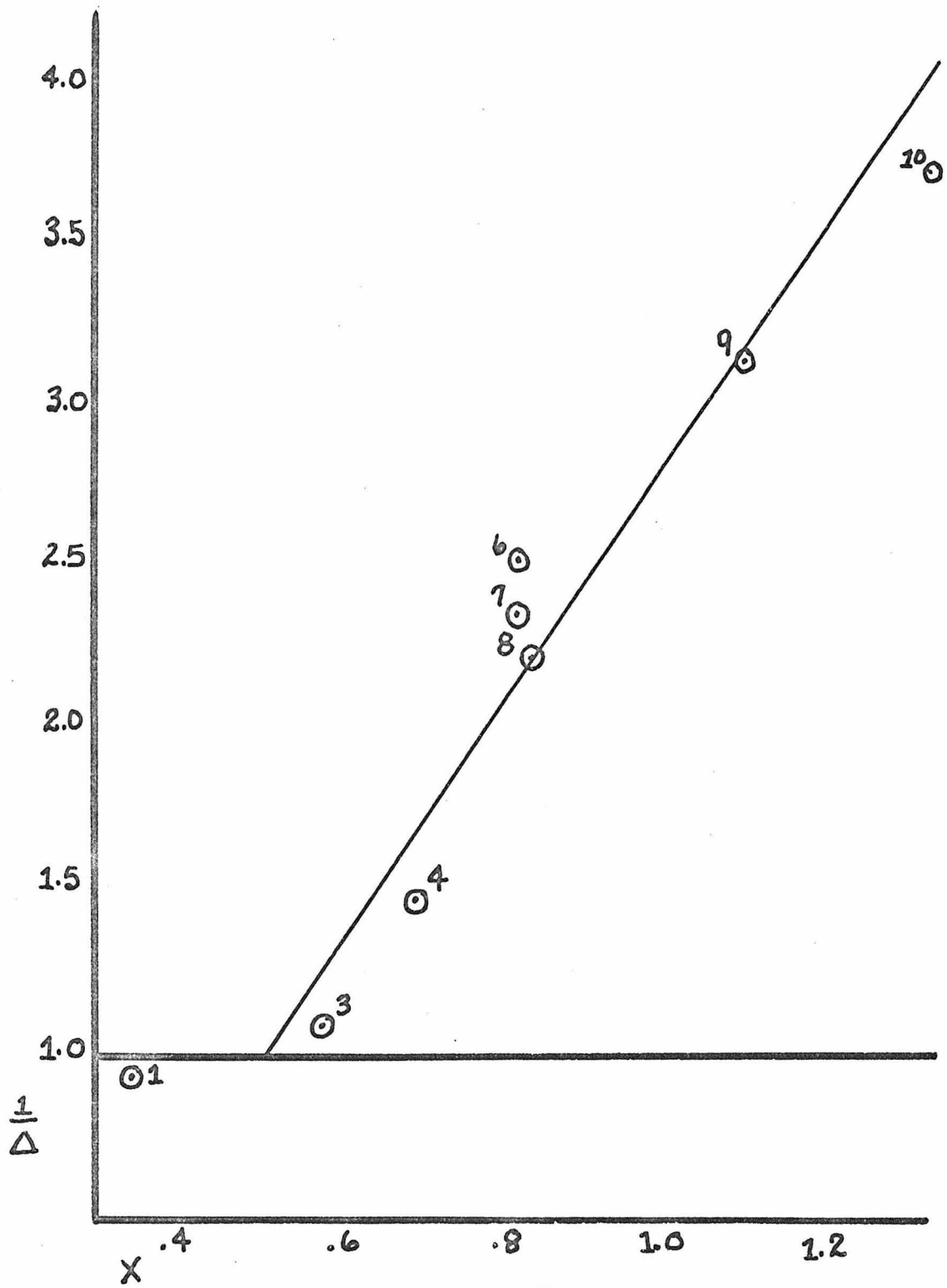
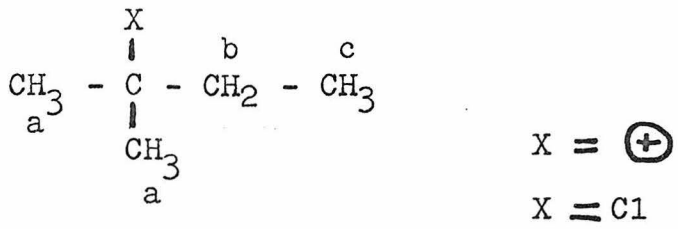


Figure 28

estimated by titration with t-butyl chloride. The data



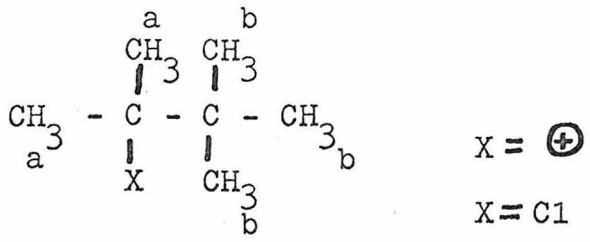
XIII

in Figure 29 indicate that in both cases t-amyl chloride is equilibrating between chloride and cation at fast exchange. This is reflected in the averaged chemical shifts and coupling constants for the two equivalent methyl groups. Assigning the percentage of cation in the two cases using the low field methyl resonance gives 56% and 61%. This also is consistent with $J_{Ha-Hb} = 3.5$ cps, indicating nearly half chloride and half cation. The singlet accounting for about 30% of the total integral is assigned to t-butyl chloride and t-butyl cation. This is confirmed by a quenching experiment in which t-butyl alcohol was produced as well as t-amyl chloride and alcohol. Cleavage of t-amyl cation to give small amounts of t-butyl cation has been previously reported (34).

Another carbonium ion for which the exchange reaction is fast is 2,3,3-trimethyl butyl cation (XIV). The data for the exchange are shown in Figure 30. The singlet in the spectrum of 2,3,3-trimethylbutyl chloride in less than one equivalent of antimony pentafluoride indicates that

	a	b	c	other
t-amyl cation	238 cps (triplet) $J_{HA-HB} = 7$cps	265 (multiplet)	105 cps (triplet	
t-amyl chloride	96 cps (singlet) $J_{HA-HB} = 0$	102 cps (quartet - two peaks under singlet)	64 cps (triplet)	
≈ 1 mmole t-amyl chloride 0.45-0.55 mmoles SbF_5	175 cps (triplet) $J_{HA-HB} = 3.0$cps	200 cps (broad multiplet)	86 cps	singlet ≈1/3 total integral 138 cps
0.77 mmoles t-amyl chloride 0.45-0.55 mmoles SbF_5	182 cps (triplet $J_{HA-Hb} = 3.5$ cps		87 cps	141 cps singlet

Figure 29



XIV

exchange between chloride and cation is fast on the nmr time scale.

One of the cations studied, methylcyclopentyl, decomposed at -78° C., when less than one equivalent of antimony pentafluoride was added. The spectrum was recorded at -70° C., -50° C., and -30° C. to verify that the broad resonances observed at -105 cps and a sharper peak at -50 cps were not the result of intermediate exchange rate between cation and chloride. The spectrum was temperature independent. Quenching experiments on the cation revealed no methylcyclopentyl alcohol. Both products formed had gas-liquid partition chromatography retention times longer than the alcohol.

Two of the cations showed slow exchange between cation and chloride. The results (for 1,2-dimethylnorbornyl cation) are shown in Figure 31. The results of the 2-methylnorbornyl cation experiment in less than one equivalent of acid are shown in Figure 32. These data show slow exchange between the 2-methylnorbornyl cation and 1-methyl-

	a	b
2,3,3-trimethyl butyl cation		164 cps (singlet)
2,3,3-trimethyl butyl chloride	100 cps	68 cps
	(average weighted for number of protons) 81 cps	
2,3,3-trimethyl butyl chloride (.96 mmoles) antimony pentafluoride (.5-.6 mmoles)		90 cps (broad singlet) 11% cation from linear interpolation

Figure 30

	methyl resonance	
1,2 dimethylnorbornyl cation	149 cps	
1,2 dimethylnorbornyl chloride	86, 62	≈33% endo
	82, 55	≈67% exo
1,2-dimethylnorbornyl chloride (1.9 moles)	145	
antimony pentafluoride (1.1 moles)	90, 65	≈40% endo
	85, 59	≈60% exo

integration gives ≈35% cation

Figure 31

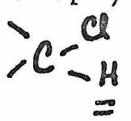
	methyl resonance	
2-methylnorbornyl cation	194 cps (singlet)	
	180 cps methylene singlet	
2-methyl-2-chloronorbornane	86 cps	
1-methyl-2-chloronorbornane	65 cps	 220 cps
2-methyl-2-chloronorbornane	194 cps	(180 cps)
0.5 equiv. antimony pentafluoride	70 cps	
	228 cps	

Figure 32

2-chloronorbornane. There is no evidence of the tertiary isomer in the spectrum, indicating that the 1-methyl-2-chloronorbornane is several kcal more stable in this solution.

Several cations were equilibrated with t-butyl cation to obtain semi-quantitative data on their relative stabilities. For each of these experiments the sealed tubes of antimony pentafluoride containing 0.3-0.5 mmoles were used. The data are summarized in Figure 33. The isopropyl doublet has a chemical shift of 88 cps in sulfur dioxide.

A few comments can be made about these data. It is clear that methylcyclopentyl cation not only decomposes, but that it also removes the antimony pentafluoride from solution. Otherwise the t-butyl resonance would be much farther downfield in the second equilibration experiment in Figure 33. It is also clear that the chloride present in the third experiment is the rearranged 1-methyl-2-chloro-norbornane. It is possible to estimate the minimum free energy differences from these experiments if we assign the maximum amount of less stable cation and minimum amount of more stable cation. These estimates are shown in Figure 34 and are based on estimated chemical shift errors or integration errors. These equilibration experiments were performed at equilibrium. This was checked with the 1,2-dimethylnorbornyl cation-t-butyl cation equilibration. The t-butyl chloride was added to the acid first, and the results were the same as for simultaneous addition. All the ions in Figure 34 are too far apart in energy to measure their relative stabilities accurately, indicating that the

Equilibration of t-Bu$^+$ and R$^+$ in 0.3-0.5 mmoles SbF_5

	mmoles t-BuCl	mmoles chloride II	t-Bu-CH_3	CH_3 chloride II	CH_3 cation II	% cation II	% t-Bu$^\oplus$
isopropyl chloride	0.347	0.350	240		97	small	100%
methyl-cyclopentyl chloride	0.356	0.310	111	cation decomposed		large	8%
2-methyl-norbornyl chloride	0.500	0.500	102	71	202	70%[a]	0%
1,2-dimethyl-norbornyl chloride	0.476	0.492	100	none obsvd.	150	>85%[b]	0%

[a] 16 CAT scans

[b] 21 CAT scans

Figure 33

cations	Keq min.	ΔG min.	minimum more stable	maximum less stable
t-butyl i-propyl	380	2.3 kcal/mole	96%	6%
t-butyl methylcyclopentyl			?	10%
t-butyl methylnorbornyl	36	1.4 kcal/mole	60%	4%
t-butyl dimethylnorbornyl	136	2.0 kcal/mole	85%	4%

Figure 34

cyclic cations are much more stable than t-butyl cation. This is especially reflected by 2-methylnorbornyl cation, where the difference in ground state free energy between the tertiary and secondary chlorides should partially offset the difference in cation stability (Figure 35). In spite of this, the equilibrium constant is still too large to be measured by this method.

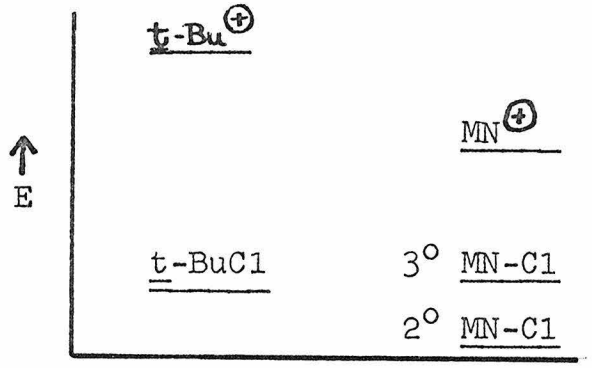


Figure 35

Two of the cations equilibrated with t-butyl cation were close enough in energy to make quantitative estimates of relative stabilities. The data for the t-amyl and 2,3,3-trimethylbutyl cation equilibrations with t-butyl cation are shown in Figure 36. Again these experiments were performed with sealed tubes, judged to contain about 0.45-0.55 moles antimony pentafluoride. It is clear from integration of the peaks for the t-butyl-t-amyl equilibration that no appreciable decomposition of t-amyl cation to t-butyl has occurred; so that the molar ratios of total

cation	area	t-butyl CH_3	t-amyl $(CH_3)_2$-C	CH_2-CH_3	% t-Bu$^+$	% t-amyl$^+$
t-butyl (0.45 mmoles) t-amyl (0.47 mmoles)	obsvd: t-butyl* 1.08 t-amyl	183 cps	211 cps (triplet J_{H-H}=5 cps (multiplet) 233 cps	90 cps	59%	81%
	calc: t-butyl 0.96 t-amyl					
t-butyl (0.47 mmoles) t-amyl (0.49 mmoles)		151 cps	193 cps	105 cps	36%	68%

*evaluated by tracing spectra and weighing

cont'd page 69

cation	mmoles	relative area obsvd: TMB / t-butyl	calc: TMB / t-butyl	t-Butyl CH_3	TMB CH_3	% t-Bu$^+$	% TMB$^+$
t-butyl 2,3,3-trimethyl-butyl	0.58 0.52	1.65*	1.53	106	115	4%	41%
t-butyl 2,3,3-trimethyl-butyl	0.51 0.55	2.08*	1.77	131	151	22%	84 %

*integral average of tracing and weighing and pk x $\frac{1}{2}$ width t-butyl singlet (9 protons): TMB singlet (15 protons)

Figure 36

t-butyl and t-amyl species is about the same. Equilibrium constants and free energy differences are shown in Figure 37.

	Keq	ΔG (in kcal /mole)	
1) t-butyl-t-amyl	3.0	0.435	av.0.48 kcal/mole
2) t-butyl-t-amyl	3.8	0.527	
1) t-butyl-TMB	16.7	1.11	av.1.14 kcal/mole
2) t-butyl-TMB	18.6	1.16	

Figure 37

The mixtures of t-amyl and t-butyl cation were quenched, and the major products were t-butyl alcohol, t-amyl chloride, and t-amyl alcohol. The t-butyl chloride could not be separated from ether on the carbowax column. Integrated areas showed the amounts of t-butyl alcohol and t-amyl alcohol to be about the same (no internal standard was used, however).

Quenching of mixtures of t-butyl cation and 2,3,3-trimethylbutyl cation with water gave t-butyl alcohol, 2,3,3-trimethyl-2-chlorobutane, and 2,3,3-trimethyl-2-butyl alcohol. The ratios of integrated areas were 0.37, 0.13, and 0.50.

Even though methylcyclopentyl cation is not stable in less than one equivalent of acid, the original cation formed did not release the antimony pentafluoride complexed

to it as the cation decomposed. It appeared that the decomposition occurred from the cation and was essentially irreversible (no methylcyclopentyl alcohol in the products of quenching). Therefore, it seemed possible to gain some idea about the original cation equilibrium by using the ≈0.3-0.5 moles of antimony pentafluoride to carry out equilibrations with methylcyclopentyl cation.

Several qualitative experiments indicated that the dimethylnorbornyl cation is more stable than the methylcyclopentyl cation. There seems to be little enough methylcyclopentyl cation present in the solution containing appreciable amounts of 1,2-dimethylnorbornyl cation that the methylcyclopentyl chloride does not decompose at an observable rate.

The results of one cation experiment with methylcyclopentyl chloride and 1,2-dimethylnorbornyl chloride in antimony pentafluoride are given in Figure 38. Methylcyclopentyl chloride in sulfur dioxide has a methyl resonance at 98 cps. The species observed are 1,2-dimethylnorbornyl cation, 1,2-dimethyl-2-<u>exo</u>- and <u>endo</u>-norbornyl chloride, and methylcyclopentyl chloride. All the resonances are farther downfield than normal, but the assignment is still clear. The ratio of methylcyclopentyl chloride to the dimethylnorbornyl species is 1.23, which compares to a molar ratio of 1.05. This is an indication that none of the methylcyclopentyl chloride has been lost

	CH_3 shift			
	dimethylnorbornyl cation - 10 protons	dimethylnorbornyl chloride - 6 ptns		methylcyclo-pentyl chloride 3 protons
0.490 mmoles dimethylnorbornyl chloride	157	106	84	113
0.516 mmoles methylcyclopentyl chloride	3.6	7.5		13.7

32% dimethyl cation/total $\qquad \frac{\text{methylcyclopentyl}}{\text{dimethylnorbornyl}} = 1.23$

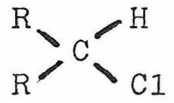
integrals by tracing and weighing from CAT spectra (20 scans)

Figure 38

by decomposition through the cation which in turn is a qualitative indication of greater stability of the dimethylnorbornyl cation

Direct equilibration of 1,2-dimethylnorbornyl and 2-methylnorbornyl cations was attempted. In two experiments on this system, the only species detected in the spectrum were the 1,2-dimethylnorbornyl cation and 1-methyl-2-chloronorbornane. In the first experiment there was still some 1,2-dimethyl-2-chloronorbornane left, as can be seen by the values of the integrals. This could not be integrated because it was superimposed on peaks from the 2-methyl-2-chloronorbornane. In the second experiment the relative integrals confirm that most of the dimethylnorbornyl species are present as the cation, and most of the methylnorbornyl species as the 1-methyl-2-chloronorbornane. These data indicate that there is a large free energy difference for the exchange reaction. An estimate for the minimum free energy difference for this equilibration is $\approx$1.4 kcal/mole. This comes from a maximum estimate of 20% for 1,2-dimethyl-2-chloronorbornane which gives a total integral for dimethylnorbornyl species of 3.9. Using the integrals in equilibration (2) of Figure 39, this leaves a maximum for methylnorbornyl cation of 10% and Keq minimum $\simeq$36.

An independent equilibration of the tertiary 2-methyl-2-chloronorbornane and the secondary 1-methyl-2-

	dimethyl cation-CH_3 resonance	integral / proton	methyl chloride CH_3 resonance	integral / proton	
(1) 2-methyl-2-chloro-norbornane (434 mg; 3.0 mmoles) 1,2-dimethyl-2-chloro-norbornane (476 mg; 3.0 mmoles) SbF_5 (240 µl; ≈3.3 mmoles)	146 cps	4.1	68 cps	8.5	224
(2) 2-methyl-2-chloro-norbornane (326 mg; 2.25 mmoles) 1,2-dimethyl-2-chloro-norbornane (356 mg; 2.25 mmoles) SbF_5 (215 µl; ≈3.0 mmoles)	142 cps	3.3	63	3.6	227

integrals were evaluated by tracing and weighing (av. of 2 determinations)

Figure 39

chloronorbornane indicated an equilibrium (i.e. no change with time) concentration of >90% tertiary isomer. Therefore, the free energy difference between the tertiary and secondary isomers is > 1.0 kcal/mole. It is impossible to tell if the 1,2-dimethylnorbornyl cation is significantly more stable than the methylnorbornyl cation because of the isomerization of 2-methyl-2-chloronorbornane.

When less acid is introduced, the rate of isomerization of 2-methyl-2-chloronorbornane is slowed to an observable rate. Dimethylnorbornyl chloride (0.515 mmoles) and methylnorbornyl chloride (0.502 mmoles) were dissolved in sulfurylchlorofluoride. The chloride solution was added to 20 μl antimony pentafluoride in sulfur dioxide. The pmr spectrum of the solution showed no dimethylnorbornyl cation, so another 20 μl of antimony pentafluoride was added. The results of the experiment are shown in Figure 40. These data are consistent with the scheme shown in Figure 41.

time after mixing	peak height - methyl					
	153 cps	106 cps	102 cps	97 cps	79 cps	72 cps
t=0	-	26	24	17	20	13
t=2 min.	14	21	18	16	22	9
t=30 min.	14	15	19	15	29	9
t=40 min.	14	15	19	16	28	8
t>40 min.	14	15	19	16	28	8

Figure 40

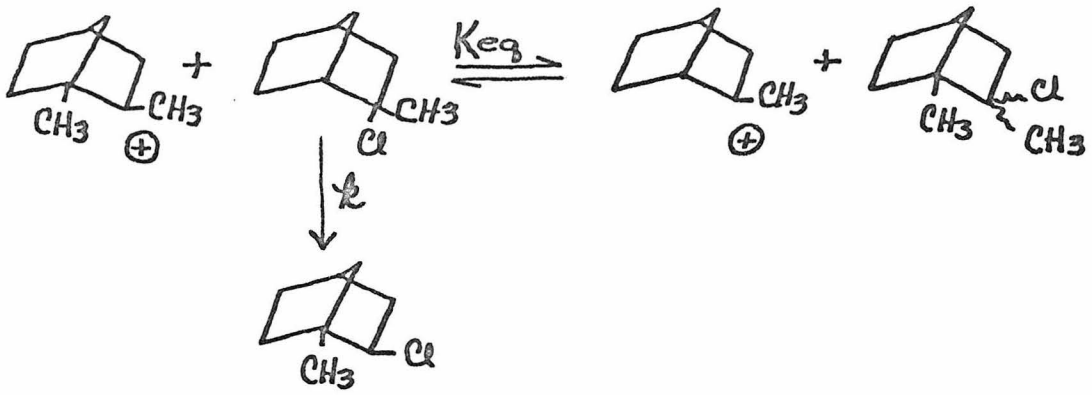


Figure 41

The methyl resonances were assigned as follows: 153 cps - 1,2-dimethylnorbornyl cation; 106 cps - 2-methyl-norbornyl chloride; 102, 97,79,and 72 cps - dimethylnorbornyl chloride, and 79 cps - 1-methylnorbornyl chloride. There was no methylnorbornyl cation visible. The integrals from the time-averaged spectrum are shown in Figure 42. The ratio of total dimethylnorbornyl species and methyl-norbornyl species (0.83) is slightly below the expected molar ratio of 0.97. The percentage of dimethylnorbornyl cation is 24%, and no methylnorbornyl cation is seen in the spectrum. This indicated that the dimethylnorbornyl cation is the more stable. If we assign the difference between stabilities of 1,2-dimethylnorbornyl cation and 2-methylnorbornyl cation to an electronic inductive effect,

	153	106	102 & 97	79 & 72
integral	40.6 40.9 41.0 40.8	27.2 26.8 26.0 26.7	39.5 40.6 40.5 40.2	56.8 56.7 57.4 57.0
integral corrected for # protons	12.3	26.7	40.2	57.0
	DMN	DMN-C1	MN-C1	
corrected integral	12.3	40.2	26.7 + (57.0 - 40.2) = 43.5	

24% DMN^+ cation total DMN/MNN .83
integrals from CAT spectrum are by tracing and weighing.

Figure 42

we predict that the equilibrium constant for the equilibration will be the same order as that for the t-butyl - t-amyl system (Keq=3.4). This means that 8% of the methylnorbornyl species will be cation. After isomerization of the tertiary methylnorbornyl chloride, the energy difference will be at least 1.4 kcal/mole (see p. 73). Thus the equilibrium constant will change from Keq=3.4 to at least Keq=35. The net result of this would be the release of the antimony pentafluoride associated with methylnorbornyl cation. The integral of the methyl groups of dimethylnorbornyl cation should increase by $\approx$ 30% relative to the integral for the methyl groups of all the chloride species. That this is not the case is seen in Figure 43.

integral	time	153 cps	106,102,97,79,and 72 cps
	2 min.	27	73
	30 min.	22	78
	40 min.	24	76
	>40 min.	25	75
	average	24 ± 5.9 (95% confidence)	76

Integrals were evaluated by tracing and weighing; numbers are the average of two determinations and are normalized.

Figure 43

DISCUSSION

It is interesting to compare results of cation equilibrations to solvolysis experiments in order to see whether the cation stabilities are reflected in solvolysis rate experiments. The expectation that the difference in cation stability and solvolysis rate ratios should correlate is borne out qualitatively in all cases but 5 and 7 in Figure 44. The solvolysis work on the substituted t-butyl system was done in 1949 by H. C. Brown. Instead of finding a simple addition of methyl inductive effects in substitution of methyl groups onto t-butyl chloride, Brown discovered that this system was more complicated. On substitution of the first methyl (t-amyl chloride) the rate of solvolysis increased. The introduction of a second methyl depressed the rate below that for t-butyl chloride, while the third methyl substitution caused a rate increase. This behavior was described in terms of changing relative magnitudes of the inductive, hyperconjugative, and steric effects. On the substitution of one methyl group, the inductive effect predominates, increasing the rate. The second methyl group decreases the rate because the hyperconjugative effect predominates, and the i-propyl group is not as stabilizing as an ethyl group. The rate goes up with the third substitution because steric stress facilitates the solvolysis (35).

cations	relative rates	ΔG kcal/mole (from rel. rates)	ΔG (equil.)
1) t-butyl - i-propyl	5.50×10^4 (a)	6.4	>2.3 (min)
2) methylcyclopentyl - t-butyl	6.53×10^1 (a)	2.5	large
3) methylnorbornyl - t-butyl	3.50×10^2 (a)	3.5	>1.4 (min)
4) dimethylnorbornyl - t-butyl	$\approx 1.7 \times 10^3$ (d)	4.4	>2.0 (min)
5) t-amyl - t-butyl	1.67 (b)	0.30	0.48
6) 2,3-dimethyl-t-butyl - t-butyl	0.88 (b)	-0.08	
7) 2,3,3-trimethyl-t-butyl - t-butyl	1.21 (b)	0.11	1.14
8) dimethylnorbornyl - methylcyclopentyl	1.88×10^1 (c) (exo isomer)	1.9	large
9) dimethylnorbornyl - methylnorbornyl	4.8 (c)	1.0	>0.5

(a) ref. 9 25° C chlorides
(b) ref. 35 25° C chlorides
(c) ref. 12 50° C p-nitrobenzoates
(d) estimated from methylnorbornyl chloride-t-butylchloride relative rate and methylnorbornyl (PNB) and dimethylnorbornyl (PNB).

Figure 44

Our cation equilibrations do not follow the order observed for the solvolyses in this particular series. The first methyl group is observed to stabilize the cation, and the second and third methyl substitutions are also stabilizing in a slightly less than additive fashion. We do not feel inclined to invoke this unusual juggling of hyperconjugative and steric effects to explain our data. We are presently studying the 2,3-dimethyl-t-butyl cation to see if it fits in our proposed progression or is less stable than t-butyl and t-amyl cation as the solvolysis experiments would predict. It is possible that the hyperconjugative and steric arguments are not necessary to explain the effect of methyl substitution on t-butyl cation stability. The results obtained so far can be correlated on the basis of increasing cation stability due to greater inductive election release by methyl groups compared to hydrogen.

The question concerning cation stabilization by methyl or methylene bridging is our main concern. The charge in 2,3,3-trimethylbutyl cation is distributed over two tertiary carbon atoms (see Figure 16). Furthermore the methyl shift which causes this charge distribution is associated with a maximum free energy barrier of 2-3 kcal/mole (18). These data suggest the possibility of stabilization of the cation through methyl bridging (Figure 45).

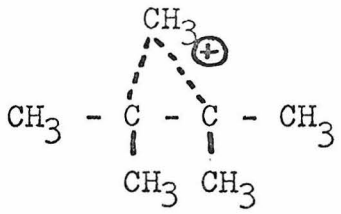


Figure 45

Such bridging would be very ineffective in t-amyl cation, because the methyl shift would generate the much less stable primary cation. Therefore the substitution of the second and third methyl group in t-butyl cation should be much more stabilizing than the substitution of the first if the nonclassical structure (Figure 45) were important. In fact, the 2,3,3-trimethylbutyl cation shows no extra stabilization over that predicted from the effect of the first methyl substitution. If the second and third methyl groups showed the same effect as the first, the free energy difference between t-butyl cation and 2,3,3-trimethyl-2-butyl cation would be 1.44 kcal/mole. The measured value is $\Delta G = 1.14$ kcal/mole. It is apparent that methyl bridging adds no extra stability to this cation even though the positive charge of the carbonium ion is distributed over two carbon atoms. This observation is in agreement with that made earlier by J. D. Roberts that the nonclassical structure does not contribute significantly in reaction of 2,3,3-trimethyl-2-butanol with hydrochloric acid (5). The same conclusion has been reached by

H. C. Brown for solvolysis and hydrochlorination reactions of 2,3,3-trimethylbutyl derivatives (6).

It is more difficult to reach a conclusion on the role of methylene bridging in the tertiary bycyclic cations. The two relative stability measurements which have application to this question are those between 1,2-dimethylnorbornyl cation and methylcyclopentyl cation or 2-methylnorbornyl cation. The most conclusive observation we can make from these measurements is that they are not consistent with our expectations for a classical 1,2-dimethylnorbornyl cation. H. C. Brown has advocated the use of methylcyclopentyl cations as a model system for classical bicyclic cations (8). Chemical shift data on ionization of methylcyclopentyl cation in antimony pentafluoride indicate that the positive charge is localized on one carbon (Figure 16). Our expectation is, therefore, that the classical 1,2-dimethylnorbornyl cation should be more stable than methylcyclopentyl cation only by virtue of a small methyl inductive effect. Such an inductive effect is $\approx$0.48 kcal/mole in t-amyl cation. Therefore, we believe the observation that methylcyclopentyl chloride competes poorly with 1,2-dimethylnorbornyl chloride for antimony pentafluoride is inconsistent with our expectations for a classical 1,2-dimethylnorbornyl cation.

The direct equilibration of 2-methylnorbornyl cation and 1,2-dimethylnorbornyl cation is more convincing. In

the absence of steric strain on introduction of a methyl group at C-1 the effect of such a substitution should be to stabilize 1,2-dimethylnorbornyl cation over 2-methylnorbornyl cation by about 0.48 kcal/mole.

Models indicate little steric strain on introduction of the methyl group at C-1. Furthermore other authors have also observed that they would expect 1-methyl-2-norbornyl alcohol to be free of substituent-induced strains (10). Finally, there are some experimental data that qualitatively indicate little steric strain on introduction of the methyl group. The methyl group is larger in terms of steric interaction than either a chloro or an hydroxyl group. This difference is reflected in the following A values: methyl; 1.5-1.9; chloro, 0.3-0.5; and hydroxyl, 0.4-0.9 (36). These values are the energy differences in kcal/mole between the axial and equatorial substituents in cyclohexane. The steric difference is also reflected in an axial-axial methyl-hydroxyl interaction of 2.2-2.4 kcal/mole and a methyl-methyl interaction of 3.7 kcal/mole (36). The most serious steric effect of a methyl substitution at C-1 would be the interaction with the substituent in the <u>exo</u> position at C-2. Therefore, if this interaction were large, an <u>exo</u> chloro or hydroxyl group would be favored over an <u>exo</u> methyl group. The net result is that in comparison to the <u>exo-endo</u> equilibria in other norbornyl

compounds, 1,2-dimethylnorbornyl compounds should show a large exo:endo ratio. Our data indicate this is not the case (Figure 46). In the absence of further evidence we will assume the ground state free energies of 2-methyl-2-chloronorbornane and 1,2-dimethyl-2-chloronorbornane are about the same.

If we assume that both 2-methylnorbornyl cation and 1,2-dimethylnorbornyl cation are classical, the equilibrium constant for their exchange should be $\approx$ 3.8. This would mean that in the equilibration experiment just after addition of acid we should have seen 8% methylnorbornyl cation and 25% 1,2-diemthylnorbornyl cation. Furthermore as 2-methyl-2-chloronorbornane isomerized to 1-methyl-2-chloronorbornane, the antimony pentafluoride associated with the 2-methylnorbornyl cation would be released, and the 1,2-dimethylnorbornyl cation would increase by one-third relative to the chloride present. Neither of these expectations was confirmed by the experiment which did not reveal the presence of any methylnorbornyl cation and did not show a significant increase in the amount of 1,2-dimethylnorbornyl cation with time. We feel that the integration procedure shown in Figure 43 is sufficiently reproducible to assure that the amount of 1,2-dimethyl-norbornyl cation increased by much less than one-third during the isomerization. Therefore the addition of the

compound	exo/endo	temp.	solvent
1,2-dimethyl-2-chloronorbornane	2	25°C.	HCl-MeOH
1,2-dimethyl-2-norbornyl alcohol	1.1	65°C.	SO_2
1,2-dimethyl-2-norbornyl alcohol	2.6[a]	25°C.	60% aq. dioxane
2-methyl-2-norbornyl alcohol	1.3[a]	25°C.	60% aq. dioxane
2-phenyl-2-norbornyl alcohol	2.1[a]	25°C.	60% aq. dioxane
2-norbornyl alcohol	4[b]	100°C.	isopropyl alcohol

[a] ref. 10

[b] ref. 37

Figure 46

second methyl group seems to give the cation a degree of stability greater than would be anticipated on the basis of inductive stabilization.

In Figure 16 there are three cations which show significant charge delocalization in the pmr spectra. Cation stability measurements indicate that methyl bridging in 2,3,3-trimethylbutyl cation is not important. Similar measurements on 1,2-dimethylnorbornyl cation indicate that methylene bridging does stabilize the cation, but the extent of this extra stabilization is unknown. Our experiments allow no decision to be made on the role of methylene bridging in 2-methylnorbornyl cation.

EXPERIMENTAL

2,3,3-Trimethyl-2-butyl alcohol

$$(CH_3)_2 - \underset{\underset{Cl}{|}}{C} - C - (CH_3)_3 \xrightarrow[H_2O]{H^+} (CH_3)_2 - \underset{\underset{OH}{|}}{C} - C - (CH_3)_3$$

2,3,3-Trimethyl-2-chlorobutane (Aldrich, sublimed) was dissolved in a mixture of acetone and water. A few drops of sulfuric acid were added as a catalyst, and the solution was heated at 80° C. for two hours. The solution was extracted with ether, and the product isolated. The product was a white solid, identified by its pmr and ir spectra as 2,3,3-trimethyl-2-butyl alcohol.

Preparation of saturated antimony pentafluoride solution

Antimony pentafluoride was placed in the reaction vessel (Figure 20). Sulfur dioxide was added to the cold vessel (-78°C.), and the vessel was heated until the solution was homogeneous. The solution was recooled to -78°C., and some of the antimony pentafluoride precipitated. This solution was allowed to stand under nitrogen for 30 minutes. Aliquots (0.5 ml) were withdrawn in syringes cooled in liquid nitrogen and fitted with teflon needles. The aliquots were placed in glass tubes, and the tubes were sealed. These tubes were stored in the freezer (-28°C.) until needed.

Equilibration in less than one equivalent of acid

The appropriate chloride was weighed into a small glass round bottom flask (2 ml) fitted with a serum cap. The flask was cooled and sulfurylchlorofluoride condensed into the vessel until the solution was homogeneous. An attempt was made to keep the volume of solution $\approx$ 0.6 ml. The 0.5 ml tube of antimony pentafluoride was placed in the reaction vessel, and the vessel was immersed in an acetone-dry ice bath. The cold solution of chloride was then added to the antimony pentafluoride solution which was vigorously stirred with nitrogen. The cation solution was withdrawn into an nmr tube which was either sealed with a torch or with a plastic cap and parafilm. Those tubes sealed with the plastic cap did not seem to pick up moisture over several days (i.e. the percentage of cation remained the same).

Quenching experiments were performed by pouring the contents of the nmr tubes into ice water and extracting the solution with ether or petroleum ether. The organic layer was washed with sodium bicarbonate and dried. The organic solution was then analyzed on a 12 foot column of 10% carbowax 20M on chrom G using a Beckman GC-5 flame ionization gas chromatograph.

In the case of 2-methylnorbornyl chloride and 1,2-dimethylnorbornyl chloride the equilibrations in less than one equivalent of acid were not carried out with the

standardized tubes of antimony pentafluoride. The procedure was the same except that an approximate amount of antimony pentafluoride was pipetted into the reaction vessel, and the sulfur dioxide solution was prepared.

Equilibration of two cations

The procedure was the same as above except that both chlorides were weighed into the 2 ml round bottom flask, dissolved in sulfurylchlorofluoride, and added simultaneously to the antimony pentafluoride solution. Where one chloride was a solid and the other a liquid, the solid was weighed into the flask, the flask was capped, the liquid introduced by microsyringe, and the flask was weighed again.

Equilibration of 2-methylnorbornyl cation and 1,2-dimethylnorbornyl cation

The experiments were carried out as before except that the tubes of standardized antimony pentafluoride were not used. Antimony pentafluoride ($\approx$20 μl) was added to the reaction vessel, and the sulfur dioxide solution was prepared. The spectrum indicated no cation species, so another 20 μl of antimony pentafluoride was added and the solution withdrawn and sealed as before. This solution was immediately placed in the spectrometer, and the nmr spectrum was recorded.

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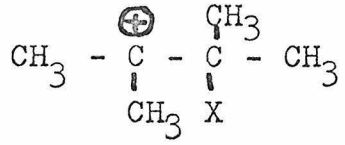
PROPOSITION I

Bridged halonium ions have been proposed for each of the halogens except fluorine. Anchimeric assistance by bromine and iodine has been established by solvolysis of 2-substituted-cyclohexyl brosylates. The trans:cis rate ratio for solvolysis of 2-bromo-cyclohexyl brosylate is 800 while the trans:cis rate ratio is only 4 for the chloro-substituted compound (1). The participation by iodine is even more striking and is estimated to provide 8.5 kcal/mole stabilization by bridging (2). There is little indication of anchimeric assistance by the chlorine substituent (1). Further evidence for the bromonium ion comes from the observation that threo-3-bromo-2-butanol gives d,l-2,3-dibromobutane on bromination while the erythro isomer gives meso-dibromobutane (3). There is also evidence that the reaction of 3-chloro-2-methylpropene with hypochlorous acid proceeds $\approx$ 38% through a symmetrical chloronium ion (4).

More recently G. A. Olah has examined the halo-substituted stable carbonium ions generated from 2-methyl-2-fluoro-3-methyl-3-halo butane in antimony pentafluoride. He argues that all but the fluoro-substituted cations are nonclassical halonium ions. This conclusion is drawn from the chemical shift difference on ionization shown below:



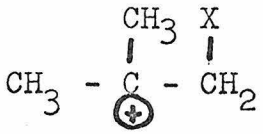
X	Δ on ionization ppm.
fluoro	-1.76
chloro	-1.15
bromo	-1.08
iodo	-1.05

This is the same order expected on the basis of electronegativity, but the authors feel the large chemical shift of the protons in the fluoro compound is indicative of much smaller amount of positive charge on halogen (5).

It is proposed that the direct equilibration of these halogen-substituted cations be carried out to determine the free energy difference between them. The observed energy difference would indicate the amount of cation stabilization from halogen bridging superimposed on the normal substituent effect. If all the ions except the fluoro-substituted ion are stabilized by halogen bridging, there should be a much larger decrease in free energy on going from chlorine to fluorine than iodine to bromine or bromine to chlorine.

It would also be interesting to prepare halogen-substituted ions(I). This would permit estimation of a normal substituent effect in the absence of halogen bridging. These two experiments would allow quantitative estimation of the amount of cation stabilization due to

halogen bridging.



I

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PROPOSITION II

It would be interesting to have some measure of the degree of ionization in solvolysis experiments relative to that of a "stable" cation in antimony pentafluoride. This might be evaluated by the degree to which a substituent is stabilizing or destabilizing in solvolyses and in equilibration of two cations. However, our experiments seem to indicate that the qualitative direction of substituent effects is not the same in the two experiments. It is possible that this is a consequence of different degrees of ionization in the solvolysis of two substituted compounds.

It is proposed that the deuterium isotope effect on solvolysis and cation equilibration of the t-butyl system be studied. It is hoped that the degree of ionization will be the same in the transition states for solvolysis of t-butyl chloride and its deuterated analogs.

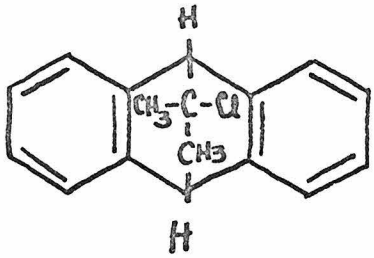
The isotope effects measured in solvolysis experiments on t-butyl chloride are shown below (1):

compound	rel. rate.
$(CH_3)_2CClCH_3$	1.00
$(CH_3)_2CClCD_3$	1.33
$(CH_3)CCl(CD_3)_2$	1.71
$(CD_3)_3CCl$	2.32

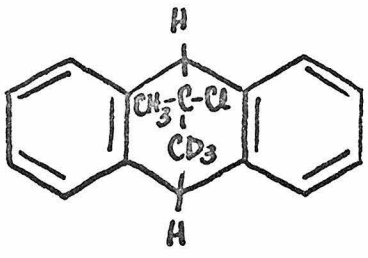
If the equilibrium constants are of the same order as the relative rates, these differences would be easily measured

by cation equilibration.

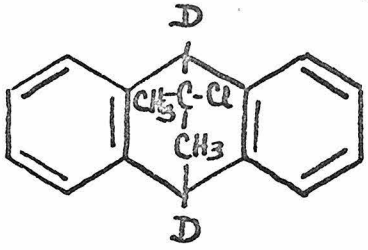
Hyperconjugation (i.e. delocalizations of C-H electron into the vacant p orbital) is the generally accepted mechanism used to explain β deuterium isotope effects. The most convincing evidence that these isotope effects are hyperconjugative in nature comes from their steric dependence. The data for solvolysis of IIa, IIb, and IIc indicate that a C-D bond directed perpendicular to an incipient p orbital does not give a β deuterium isotope effect. This is in agreement with the theory of hyperconjugative origin of these effects (2).



IIa



IIb



IIc

	kH/kD
IIb	1.14
IIc	0.986

The isotope effect arises from stretching the C-H bond by overlap with the p orbital. The magnitude of this

bond weakening and therefore the isotope effect should depend on the amount of positive charge and the extent of overlap (3).

We feel therefore that the magnitude of the deuterium substituent effect on cation stability should be a good indication of the amount of positive charge in stable cations relative to solvolysis transition states.

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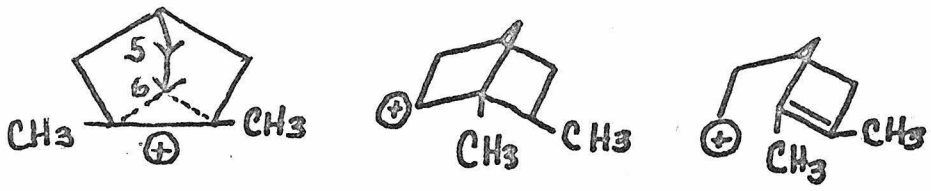
PROPOSITION III

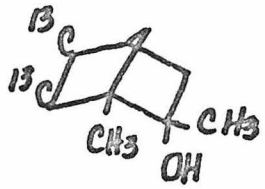
G. A. Olah has shown that ^{13}C-H coupling constants for carbonium ions are related to the hybridization at a particular carbon atom. The coupling constant for two carbonium ions is ≈126 and 128 cps, while for the precursor hydrocarbons J ^{13}C-H =168 and 164 cps. These coupling constants give calculated s character values of 25.2 and 25.6% and 33.6 and 33.8% respectively in good agreement with the predicted sp^2 and sp^3 hybridization (1). Recently it has become possible to measure ^{13}C chemical shifts and ^{13}C-H coupling constants from natural abundance ^{13}C nmr spectra of neat solutions (1).

The resonance assigned to the C-6 protons of dimethylnorbornyl cation is 80 cps downfield of that for the C-5 proton. It is possible that this is a result of charge delocalization to C-6 by a 1,6 hydride shift or by resonance delocalization.

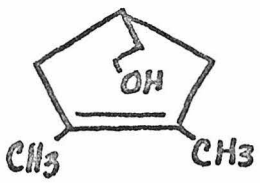


It is proposed that ^{13}C enriched ethylene be used to prepare 1,2-dimethyl-2-norbornyl alcohol, and that the

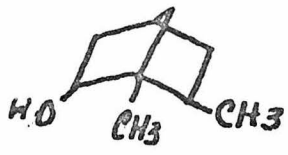
^{13}C chemical shifts and ^{13}C-H coupling constants at C-5 and C-6 be compared in the alcohol and cation. If our original



proton assignments were correct, we would expect the C-6 resonance to occur downfield of C-5 after ionization due to positive charge at the C-6 position. Since ^{13}C chemical shifts are much larger than proton shifts, the downfield shift for ^{13}C should be more striking than for protons. It also should be possible to tell if there is any appreciable change in hybridization of C-6 (relative to C-5) on ionization of the alcohol from the ^{13}C-H coupling constant. This would give an indication of any appreciable change toward sp^2 hybridization at C-6. If on ionization there is a change to sp^2 hybridization, it would be interesting to do a careful product study on the cation quench solution, looking for the following compounds:



or



This would indicate whether delocalization by 1,6 hydride shift or resonance delocalization were more important.

By proton decoupling of the ^{13}C nmr spectrum it also would be possible to confirm the proton chemical shifts for the cation.

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PROPOSITION IV

Carbonic anhydrase is a metal containing enzyme which catalyzes the hydration of carbon dioxide. It has been shown recently by differential infrared analysis that carbon dioxide bound to the enzyme is not coordinated to the zinc (II). Ionic inhibitors of the enzyme reaction such as N_3^- and HCO_3^- seem to be bound to the zinc (II), and both displace carbon dioxide from the binding cavity of the enzyme (1). This enzyme also catalyzes the hydration of several aliphatic aldehydes and is inhibited by aliphatic alcohols, SNC^-, N_3^-, and acetazolamide (2). The zinc can be replaced by cobalt (II) and enzyme activity is still preserved (1,2). Since the zinc is not involved in substrate binding, its proposed role is the coordination of the water molecule which attacks the substrate (2). It is proposed that study of the cobalt (II) enzyme be carried out to determine if the inhibitors of this enzyme displace water in the first coordination sphere of the cobalt, and if these inhibitors are bound directly to the cobalt. This will not unequivically establish the role of the metal ion in the reaction, but it will indicate whether it is likely that its role is coordination of the water used in hydration of carbon dioxide or aldehydes.

The alcohol inhibitors are subject to investigation of broadening of the nmr proton resonances due to coordina-

tion to paramagnetic cobalt (II) ion. In the fast exchange limit for enzyme substrate interaction in the nmr, it is possible to calculate an upper limit for separation of the inhibitor protons from the manganese (II) in manganese-carboxypeptidase. From the observed broadening in the nmr spectrum of methoxyacetic acid, it was determined that this molecule is directly coordinated to the metal, i.e. in the first coordination shell (3). By applying this procedure to the alcohol inhibitors of carbonic anhydrase, it may be possible to show whether these are coordinated to cobalt.

Furthermore, investigation of the water protons by nmr in the presence of the ionic and organic inhibitors may reveal whether these are displacing water from cobalt. In manganese (II)-CPD, the water signal is very broad when a mixture of $Mn \cdot (H_2O)_6$ and Mn-CPD, is examined. This is due to binding of water to the paramagnetic manganese ion. When inhibitor is added, the signal sharpens because water is displaced from the Mn-CPD. From the temperature and concentration independence of T_1 and T_2 and the magnitude of broadening, the authors were able to say that a water molecule is displaced from the primary coordination shell of manganese in Mn-CPD (4). A similar experiment is proposed for inhibitors of cobalt carbonic anhydrase. These experiments would give further indication of the

role of the metal ion in the binding of water and inhibitors to carbonic anhydrase.

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PROPOSITION V

An interesting feature of substrate binding to acetylcholine esterase is the requirement for a positively charged group on the substrate. Such positively charged substituents are thought to induce conformational changes upon binding to ACE. In the phosphorylation of ACE by phosphates with charged and uncharged leaving groups, Wilson, et al. have concluded that the positively charged leaving groups may complex with the enzyme causing a conformation change in ACE (1). Catalysis of sulfonation of ACE by substituted ammonium ions also suggests a conformational change induced by these ammonium activators (2). Changeux found that at low ionic strength flaxedil, a "reversible" inhibitor of ACE, is only partially competitive with substrate. This suggests another binding site on ACE which might promote allosteric conformational changes (3). Derivatives of aminonaphthalenesulfonic acids do not fluoresce in water but do so when bound to hydrophobic sites on enzymes (4,5). It is proposed that such compounds be used as fluorescent indicators of substrate and inhibitor induced conformational changes in ACE.

It would be of interest to bind charged ammonium compounds in order to determine if the binding of such compounds is competitive with fluor binding and if binding of these inhibitors or activators quenches fluorescence.

Such quenching is taken as an indication of conformational changes induced by the binding of inhibitors (5). Similar studies would be carried out using flaxedil under conditions of low ionic strength to test Changeux's suggestion that such binding induces allosteric transition.

Enzyme acylation should also be studied to see if acylation is competitive with fluor binding and if there is a conformational change occurring during acylation. Such a change has been postulated for α-chymotrypsin (6). Finally the pH dependence of the fluorescence of the fluor-enzyme complex can be determined to probe the environment of the enzyme-fluor binding site.

The development of a fluorescent substrate such as fluor-$\overset{O}{\overset{\|}{C}}$-O choline might permit formation of fluorescent labelled acyl-enzyme. This would permit studies of the environment of the active site.

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